UNIVERSIDAD AUTÓNOMA DE MADRID

FACULTAD DE MEDICINA

DEPARTAMENTO DE CIRUGÍA

TESIS DOCTORAL

"ENFERMEDAD INMUNOMEDIADA DEL OÍDO INTERNO: CONTRIBUCIÓN DE NUEVAS HERRAMIENTAS DIAGNÓSTICAS PARA SU CARACTERIZACIÓN."

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CERTIFICAN:

Que Dª. ITHZEL MARÍA VILLARREAL PATIÑO, natural de Cali, Colombia, con N.I.E Y-1304532 D Licenciado en Medicina y Especialista en Otorrinolaringología, ha trabajado bajo nuestra dirección en la elaboración de su Tesis Doctoral: "ENFERMEDAD INMUNOMEDIADA DEL OÍDO INTERNO: CONTRIBUCIÓN DE NUEVAS HERRAMIENTAS DIAGNÓSTICAS PARA SU CARACTERIZACIÓN", considerando que se encuentra en las debidas condiciones para su defensa ante el Tribunal que proceda.

Madrid, a 1 de noviembre de 2017

Fdo: J.R. GARCÍA-BERROCAL **Fdo: C. LÓPEZ-CORTIJO**

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ABREVIATURAS Y ACRÓNIMOS:

AECA Anticuerpos anticélulas endoteliales

ANA Anticuerpos Antinucleares

ANCA Anticuerpos Anticitoplasma de Neutrófilos

Anti-TNF Anti-Tumor Necrosis Factor

AP-1 Proteína activadora 1

AR Artritis Reumatoide

ATL Audiometría Tonal Liminar

AZA Azatioprina

C-ANCA Anticuerpos Anticitoplasma de Neutrófilos Patrón Citoplasmático

C3 Complemento 3

C4 Complemento 4

CMH Complejo mayor de histocompatibilidad

dB Decibelios

EIOI Enfermedad inmunomediada del oído interno

FDG 18-fluoro-2-desoxiglucosa

FDA (Food and Drug Administration)

FR Factor Reumatoide

GC Glucocorticoide

Gd Gadolinio

HLA “Human Leukocyte Antigen”

HNS Hipoacusia Neurosensorial

HNSF Hipoacusia Neurosensorial Fluctuante

HNSP Hipoacusia Neurosensorial Progresiva

HNSS-R Hipoacusia Neurosensorial Sordera Súbita de Repetición

HSP70 Heat Shock Protein 70

HUPH Hospital Universitario Puerta de Hierro-Majadahonda

Ig A Inmunoglobulina A

Ig G Inmunoglobulina G

IL Interleucina

IM Intramuscular

INF Interferón

IV Intravenoso

K Potasio

Kg Kilogramos

KLH “Keyhole Limpet Hemocyanin”

LES Lupus Eritematoso Sistémico

Mg Miligramos

Na Sodio

NK “Natural Killer”

OD Oído derecho

OI Oído izquierdo

ORL Otorrinolaringología, Otorrinolaringológico/a.

PAN Panarteritis nodosa

PCR Proteína C Reactiva

PET “Positron Emission Tomography” / Tomografía por Emisión de Positrones (siglas en inglés)

PMN Polimorfonucleares

PTA “Pure Tone Average”

RM Resonancia Magnética

TC Tomografía Computarizada

TNF-α “Tumoral Necrosis Factor α” / Factor de Necrosis Tumoral (por sus siglas en inglés)

SC Subcutánea

SNC Sistema Nervioso Central

SUV Standardized Uptake Value (por sus siglas en inglés)- Valor de captación estándar

VSG Velocidad de Sedimentación Globular

SUMMARY

The main goal of this investigation is to provide a new insight towards possible diagnostic tools such as Magnetic Resonance Imaging (MRI) and PET scan (Positron Emission Tomography) to characterize immune-mediated inner ear disease (IMIED).

A retrospective case review study design, analyzing patients with IMIED was carried out. Sixty-seven patients suspected of having an IMIED (primary or secondary) were studied. Twenty-eight patients referred a sudden hearing loss as form of presentation and 39 a fluctuating hearing loss. Twenty-seven patients underwent an MRI of the temporal bone with previous intratympanic Gadolinium observing endolymphatic hydrops (EH) in 13 patients. A PET scan was performed on 30 patients being altered in 17 of them. Initial and treatment for recurrences included mainly corticosteroids: intratympanic, intravenous, oral or the combination of two or three of them.

IMIED lacks a specific serological marker and it may show different clinical presentations, mimicking diverse inner ear disorders. Fluctuating hearing loss has been the most frequent presentation in the present study. Intratympanic gadolinium (IT Gd) MRI has reported EH in a group of patients mainly affected by primary IMIED. PET has provided the diagnosis of unknown or underestimated secondary IMIED.

In conclusion, both IT Gd MRI and PET have shown to be diagnostic tools that can facilitate the characterization of this entity.

1. INTRODUCCIÓN

1.1 Definición

La enfermedad inmunomediada del oído interno (EIOI) es un síndrome definido como una pérdida bilateral neurosensorial de la audición, usualmente asimétrica, rápidamente progresiva a lo largo de semanas o meses que responde a tratamiento con corticoesteroides y/o agentes inmunosupresores. La hipoacusia puede aparecer de manera unilateral y brusca, lo que la haría indistinguible de una sordera súbita, o tener un carácter fluctuante que, cuando está acompañada de vértigo, sería muy difícil diferenciarla de una Enfermedad de Menière. La importancia de este tipo de hipoacusia radica en el hecho de que representa una de las pocas causas de sordera neurosensorial que es reversible con tratamiento médico[1-7].

1.2 Concepto de autoinmunidad

La autoinmunidad consiste en un fallo del organismo a la hora de reconocer sus propios constituyentes, por lo que se desencadena una reacción inmunitaria contra las propias células y tejidos.

Se consideran por lo general tres niveles de evidencia de una etiología autoinmune: directa, indirecta y circunstancial [8]

- Evidencia directa: Las lesiones características de la enfermedad deben ser transmitidas de humano a humano, o de humano a animal.
- Evidencia indirecta: Implica la recreación de la enfermedad que ocurre en el humano en un modelo animal. Esta categoría engloba la mayoría de las enfermedades autoinmunes.

- Evidencia circunstancial: Ocurre cuando no se puede definir una enfermedad autoinmune basándonos en una evidencia directa o indirecta.

  Se utilizan distintos marcadores orientadores como son: tener una historia familiar de enfermedad autoinmune, presencia de otras enfermedades autoinmunes conocidas en el mismo paciente [9], presencia de un infiltrado de células mononucleares en tejidos afectados, predominancia de algunos alelos del complejo mayor de histocompatibilidad (CMH) de clase II, niveles elevados de autoanticuerpos Ig G, depósitos de complejos antígeno-anticuerpo en el órgano o tejido afectado o mejoría de la clínica con el uso de corticoides o inmunosupresores.

McCabe[2], describe la primera serie de pacientes con hipoacusia neurosensorial progresiva bilateral y unos test inmunológicos alterados, que responde a un tratamiento inmunosupresor (dexametasona y ciclofosfamida).

1.3 Tipos y diagnóstico de la EIOI

La EIOI puede hacer referencia a una patología restringida al oído (EIOI primaria) o a una enfermedad sistémica autoinmune que involucra al oído interno (EIOI secundaria).[7] La EIOI es una patología poco frecuente y representa un reto otológico por la falta de pruebas diagnosticas definitivas.[10]

El diagnóstico y el manejo se basan usualmente en una evaluación audiométrica y en síntomas clínicos característicos. No existe una prueba “Gold standard” para el diagnóstico de la EIOI, así como tampoco contamos con una prueba fiable que nos evalúe el estado en el que se encuentre la enfermedad en un momento dado.

Diversas proteínas cocleares que funcionan como “objetivos inmunes” basándonos en modelos experimentales animales sobre la laberintitis inmunomediada han sido identificadas durante la búsqueda de un marcador específico.[6]

Se han desarrollado trabajos en modelos de laberintitis autoinmune como los de García Berrocal et al.[11] dirigidos a mejorar el conocimiento sobre la respuesta inmunológica del oído interno y otros como los de Harris y Sharp, para demostrar anticuerpos específicos del oído interno aplicando la técnica de Western-blot.[12] Es por lo tanto imprescindible aclarar si nos enfrentamos a una enfermedad inmunomediada aislada del oído interno (primaria) o si es una pérdida de audición autoinmune asociada a enfermedades sistémicas con un sustrato inmunológico (secundaria).

Otro abordaje diagnóstico a la EIOI, teóricamente más directo, es el estudio por imagen. Sin embargo, las imágenes sobre anormalidades cocleares, vestibulares y del VIII par craneal continúan siendo un desafío.[2,3]

No obstante, un ejemplo de una magnifica herramienta diagnóstica que puede ser utilizada en la práctica clínica y la investigación es la Resonancia Magnética (RM) del oído interno. Cuando sus imágenes se realzan con Gadolinio (Gd), la intención es revelar los espacios perilinfáticos a lo largo del laberinto membranoso de la rampa timpánica y la rampa vestibular así como de los canales semicirculares.[3,4,6,13-15] La visualización “in vivo” del aumento de tamaño del espacio endolinfático en pacientes diagnosticados de enfermedad de Menière, representa un verdadero avance en el diagnóstico de esta entidad y soporta que la RM con Gd intratimpánico puede ser una herramienta muy útil para el estudio del oído interno y sus afectaciones entre las cuales encontramos la EIOI.[3]

Por otro lado, la Tomografía por Emisión de Positrones (conocida como PET por sus siglas en ingles) es una excelente herramienta diagnóstica no invasiva que funciona realizando una reconstrucción computarizada de imágenes transversales detectadas por cristales de dos fotones (rayos gamma) liberados en direcciones opuestas después de la emisión de positrones a través de radioisótopos para crear una imagen. En el PET existen varios radioisótopos y sustratos químicos que pueden ser utilizados entre los que se encuentra la 18-fluoro-2-desoxiglucosa (FDG), el cual detecta el metabolismo de la glucosa en el tejido humano.[3,16-18]

Este examen puede evaluar la actividad de la enfermedad y el pronóstico en algunas enfermedades autoinmunes como el Lupus Eritematoso sistémico. Así el PET con FDG ha demostrado la posibilidad de visualizar grandes concentraciones de granulocitos infiltrantes, macrófagos tisulares y linfocitos activados en órganos linfoides donde la presentación de antígenos ocurre teniendo como objetivo el incremento de glucosa que ocurre en estas localizaciones.[18]

Otra hipótesis planteada en el presente trabajo se basa en la idea en la cual la FDG puede ser utilizada en PET para evaluar la actividad que ocurre en los distintos órganos de pacientes con EIOI.

1.4 Importancia médica de la EIOI

La importancia médica de la EIOI radica en el hecho de que representa una de las pocas causas de hipoacusia neurosensorial reversibles con tratamiento médico. Otras enfermedades del oído interno como la enfermedad de Menière,

que en un 25-30% de los casos tiene un origen autoinmune[6,7,11,14,19,20], o la sordera súbita, en las que se sospecha un origen inmunomediado en un subgrupo de pacientes, tras realizar un seguimiento clínico prolongado, comparten un mecanismo de lesión final común, la apoptosis de las células del oído interno con la ototoxicidad, el envejecimiento auditivo o el trauma acústico.

1.5 Relevancia socioeconómica de la EIOI

La EIOI es una enfermedad potencialmente reversible. Su relevancia socioeconómica va asociada al ahorro en recursos sanitarios, destinados a la adaptación de audífonos, implantes cocleares o de tronco cerebral, y sociolaborales, ya que se evita la pérdida de días de trabajo o puestos de trabajo por discapacidad, gracias a la recuperación precoz de un déficit sensorial tan importante para la comunicación humana y una normal interacción personal o laboral.[1,21]

Prueba Diagnóstica	Coste (€)
Inmunoglobulinas Ig A, Ig G , Ig M	16.54
Hemograma	18.08
Inmunofenotipo de linfocitos sanguíneos	30.56
Factores C3 y C4	41.35
Western blot frente a HSP 70	41.47
Ac Fluorescente antitreponema	55.60
Audiometría tonal liminar	90.22
RNM	676.69

Tabla 1. Costes de pruebas diagnósticas utilizadas en la EIOI. [21].

1.6 Epidemiología

No se conoce con exactitud la incidencia de la EIOI. Esto es debido a que no existe una prueba diagnóstica definitiva y por no considerarse como enfermedad de declaración obligatoria en nuestro país, al igual que sucede con la sordera súbita. Se ha sugerido que es más frecuente en el sexo femenino y generalmente debuta entre los 20 y los 50 años de edad, siendo poco frecuente que aparezca en la infancia.

Una reacción autoinmune puede tener un efecto lesivo en la cóclea y puede iniciarse por un ataque autoinmune[22,23] o cuando el sistema inmunitario trata de proteger el oído interno frente a una infección u otra agresión externa.

1.7 Inmunopatología

Cabe resaltar que teniendo en cuenta que el oído interno no puede ser biopsiado, para la evaluación de su patología, se han podido realizar estudios del hueso temporal en humanos con enfermedades autoinmune (síndrome de Cogan, Lupus eritematoso sistémico, granulomatosis de Wegener y poliarteritis nodosa). Los hallazgos que hasta el momento se han descrito en estos estudios involucran dos mecanismos patogénicos distintos: 1) fibrosis y osteogénesis que aparecen en los estadios finales de la inflamación, y 2) atrofia celular en ausencia de inflamación secundarios a una vasculopatía inespecífica y cambios isquémicos[24-27]

1.8 Tratamiento

1.8.1. Corticoides

- Mecanismo de acción

Los glucocorticoides actúan en varios puntos de la cascada inmune, incluyendo el reconocimiento y producción de linfoquinas (citoquinas linfocitarias). Su efecto inmunomodulador se debe principalmente a su capacidad para bloquear la función de determinados factores de transcripción como la proteína activadora 1 (AP-1) y el factor nuclear potenciador de las cadenas ligeras kappa de los linfocitos B activados (NF-kB) que participan de manera fundamental en la expresión de citoquinas pro-inflamatorias por parte de los linfocitos T (IL-2) y de los macrófagos (IL-1β y TNF-α).[28-30]

- Efectos secundarios

En la tabla 2 se presentan los efectos adversos posibles en pacientes en tratamiento con glucocorticoides resaltando aquellos que han sido observados en pacientes con EIOI. Los efectos adversos graves en pacientes con EIOI únicamente se han observado en un 0-0,9%, siendo ligeramente más frecuentes cuando se realiza un tratamiento con pulsos intravenosos de corticoides a dosis elevadas.[1]

Toxicidad Metabólica	Trastornos Endocrinos	Toxicidad dermatológica	Toxicidad Gastro-intestinal	Toxicidad Musculo-esquelética	Toxicidad Neuro-psiquiátrica	Toxicidad cardiovascular	Otros
Hiperglicemia/Diabetes Mellitus	Supresión del eje hipotálamo-hipofisario-suprarrenal	Hirsutismo, alopecia	Úlcera péptica, perforación intestinal *	Miopatía, osteoporosis, osteonecrosis *	Depresión	Hipertensión Arterial	Oculares: -Catarata subcapsular posterior -Glaucoma
Obesidad	Retraso del crecimiento	Acné, estrías	Pancreatitis, esteatosis hepática	Rotura tendinosa, artritis, artralgias transitorias	Psicosis	Ateroesclerosis acelerada	Reacciones de hipersensibilidad -Urticaria -Anafilaxia
Hiperlipidemia/ hipocalemia	Trastornos menstruales	Atrofia cutánea, equimosis, púrpura esteroidea	Hemorragia gastrointestinal	Síndrome de supresión de corticoides	Convulsiones	Arritmias Ventriculares Muerte súbita	Aumento de incidencia de infecciones
Retención hidrosalina		Retraso en la cicatrización de heridas			Pseudotumor cerebral		

Tabla 2. Cuadros resaltados en turquesa son los efectos adversos que han sido observados con mayor frecuencia en pacientes con EIOI.[1]

1.8.2 Metotrexato

El Metotrexato es un antagonista del ácido fólico. Inhibe la síntesis de los nucleótidos pirimidínicos y purínicos del ADN y el ARN impidiendo la proliferación de los linfocitos T activados.

1.8.3 Azatioprina

La Azatioprina consiste en un profármaco, emparentado con la 6-mercaptopurina que se usa como agente inmunosupresor. Se utiliza como antimetabolito inmunosupresor sólo o, generalmente en combinación con otros agentes (normalmente corticoesteroides). Se ha utilizado en enfermedades sistémicas tales como la enfermedad de Crohn, la colitis ulcerosa, la hepatitis autoinmune, la esclerosis múltiple y otras enfermedades.

1.8.4 Terapias biológicas

Según la FDA (Food and Drug Administration), se denominan agentes biológicos aquellos agentes sintetizados a partir de productos de organismos vivos aplicables al diagnóstico, prevención o tratamiento de una enfermedad o condición de los seres humanos. Se clasifican según sus mecanismos de acción (inhibidores del TNF-α, antagonistas de la IL-1, etc.).

Cada nombre de estas moléculas tiene una porción final que hace referencia a su estructura como, por ejemplo:

"-cept": se ha fusionado un receptor a la región Fc de la Ig G1 humana.

"-mab": anticuerpo monoclonal (desarrollado desde una célula híbrida que es el resultado de la fusión de un clon de linfocitos B, descendiente de una única célula madre y una célula plasmática tumoral).[1]

Los inhibidores del TNF han sido los más utilizados. El TNF consiste en una citoquina proinflamatoria producida por múltiples células, en especial los macrófagos. Promueve la inflamación activando dichos macrófagos, los neutrófilos y las células NK, aumentando la permeabilidad vascular, entre otras funciones. Se expresa en diferentes estructuras del oído interno de forma precoz durante la respuesta inflamatoria.

Algunos ejemplos de estos fármacos incluyen: anticuerpos monoclonales dirigidos contra el TNF-α quiméricos (Infliximab), humanizados (CDP571) o humanos (Adalimumab) y moléculas portadoras de fracciones solubles del receptor del TNF-α, p75 (Etanercept).

El Adalimumab ha sido empleado con éxito en un paciente con hipoacusia neurosensorial de origen autoinmune asociada a artritis reumatoide.[31]

1.8.5 Rituximab

El Rituximab es un anticuerpo monoclonal quimérico murino/humano antagonista del receptor CD20 de los linfocitos B. Varios estudios recientes han ensayado Rituximab en pacientes con EIOI y han obtenido una alta tasa de respuesta.[32,33]

2. PRESENTACIÓN CLÍNICA

2.1. Formas clínicas de presentación

En general se reconocen 4 formas clínicas de presentación:

1. Hipoacusia bilateral asimétrica y progresiva (semanas a meses) (HNSP)
2. Hipoacusia neurosensorial súbita; mas de dos episodios al año (horas a días)
3. Hipoacusia fluctuante unilateral secundaria a una afectación contralateral (meses a años) (HNSF)
4. Enfermedad de Menière Inmunomediada (bilateral)

Con el tiempo, en la mayoría de los casos, en la EIOI se terminan afectando ambos oídos y la evolución es hacia un progresivo deterioro de la audición, si no se establece un diagnóstico y tratamiento adecuado.

Se sospecha una EIOI, en la forma de presentación súbita, cuando se cumplen tres criterios mayores o bien dos mayores y dos menores.

Criterios mayores	Criterios menores
Hipoacusia bilateral	Hipoacusia unilateral
ANA >1:80	Joven o de mediana edad
Enfermedad autoinmune sistémica	Mujer
Tasa de recuperación auditiva mayor al 80%	Tasa de recuperación auditiva menor al 80%
Disminución de la células T nativas	

Tabla 3: Criterios clínicos diagnósticos para la EIOI de presentación súbita.[34]

2.2. Diagnóstico de la EIOI

El diagnóstico se basa fundamentalmente en la evaluación clínica, la demostración de una hipoacusia neurosensorial progresiva en controles audiométricos realizados periódicamente y en la respuesta al tratamiento con fármacos inmunomoduladores, como los corticoesteroides, aunque dicha respuesta es muy variable. Una vez descartadas otras causas de hipoacusia neurosensorial, se realiza una batería de pruebas inespecíficas comunes al estudio de otras enfermedades autoinmunes: hemograma, bioquímica, y la velocidad de sedimentación globular (VSG).

En algunos casos, los estudios serológicos pueden detectar algunos autoanticuerpos específicos; sin embargo, no existen pruebas serológicas o inmunológicas lo suficientemente sensibles y específicas para establecer un diagnóstico definitivo.

También se estudiaron los cambios en las poblaciones linfocitarias en sangre periférica o el papel de los inmunocomplejos en la EIOI en numerosas publicaciones.[5,19,35-37]

En la EIOI es necesario identificar autoanticuerpos que puedan actuar como marcadores de determinados subgrupos de pacientes que difieren en el pronóstico o en la respuesta a la terapia. La EIOI continúa representando un reto diagnóstico, sobre todo en la forma primaria, ya que no existen marcadores específicos. La búsqueda de autoanticuerpos específicos es esencial para mejorar el diagnóstico de la EIOI. Sin embargo, los autoanticuerpos son relativamente frecuentes en humanos sin enfermedad autoinmune.

Por ese motivo, las pruebas de imagen nos abren una puerta nueva a una posibilidad diagnóstica o al menos orientativa de la EIOI.

2.3. Estudio Inmunológico

Hasta el momento, numerosos estudios experimentales y de laboratorio se han realizado intentando discernir la respuesta inmune que ocurre en el oído interno. Estos estudios han buscado definir un perfil que caracterice a la hipoacusia inmunomediada teniendo en cuenta tanto pruebas serológicas (inmunoglobulinas, VSG, parámetros inmunológicos específicos) como la clínica, pero no han tenido resultados concluyentes.

García-Berrocal et al[38] estudiaron a 125 pacientes con el diagnóstico de enfermedad inmunomediada y concluyeron que la clínica, la presencia de ANA y anormalidades en subpoblaciones de las células T junto con la respuesta a corticoides pueden ayudar a orientar de la mejor manera el diagnóstico de la EIOI pero no encontraron un marcador inmunológico especifico.

Un estudio sistemático de la literatura realizado por Lobo et al.[13] basándose en los resultados de un total de 679 pacientes diagnosticados de hipoacusia inmunomediada, reclutados en 25 estudios revisados, observaron tal diversidad en ellos que concluyeron que la pérdida de audición inmunomediada dependía de muchos factores, no encontrando marcadores específicos.

Debido a que no es posible biopsiar el oído interno durante el curso de la enfermedad ya que esto supondría la pérdida de su función, y a que se disponen de muy pocos estudios de necropsias, mayoritariamente de pacientes con enfermedades autoinmunes sistémicas[24], se han desarrollado distintos

modelos animales de laberintitis autoinmune para conocer la patogenia de la EIOI.[11] Un ejemplo es el modelo de laberintitis experimental mediante suero homólogo o heterólogo frente al tejido coclear donde se observaron alteraciones histopatológicas en los cobayas inmunizados con tejido homólogo coclear. Se han objetivado resultados variables, desde ausencia de cambios histopatológicos en la cóclea hasta el desarrollo de un hídrops endolinfático, edema, hemorragia e infiltrados inflamatorios perivasculares.[39]

El modelo de laberintitis experimental por *keyhole limpet hemocyanin* (KLH) o laberintitis estéril en rata y en cobaya mediante la inoculación de KLH ha permitido conocer que el oído interno no es un órgano inmunológicamente aislado.[40,41]

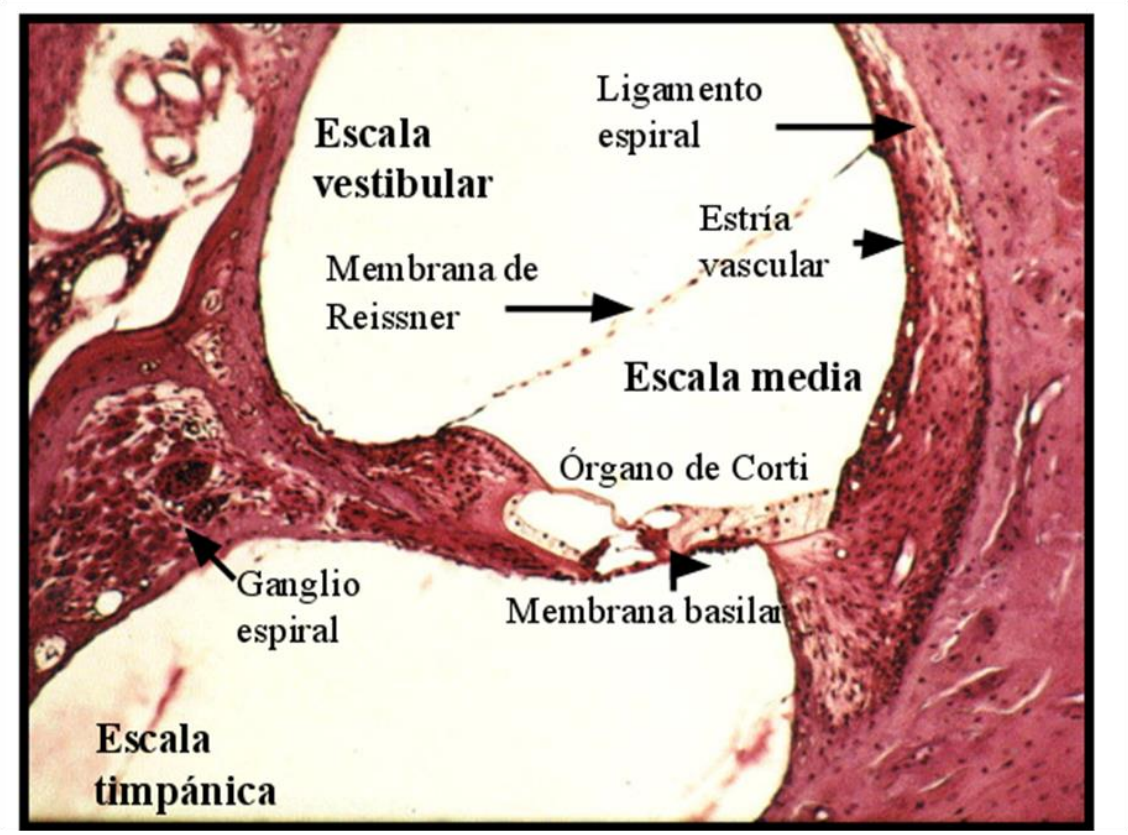

Figura 1: Microfotografía de la cóclea de cobaya. Esquema de representación del Órgano de Corti en el interior del conducto coclear [42]

Se conoce que la vena espiral del modiolo es el sitio de entrada de elementos inmunológicos (células T, células B, células NK, leucocitos polimorfonucleares, macrófagos)[39,43] que pueden llevar al desarrollo de una laberintitis especifica que finalmente genera fibrosis y osteoneogénesis coclear, consecuencia de una alteración funcional con pérdida de células sensoriales.[44-46]

Por otro lado se conoce que el epitelio del saco tiene capacidad de secretar Ig A la cual se puede encontrar en la perilinfa y el saco endolinfático además contiene células del sistema inmune capaces de producir o reforzar una respuesta inmunitaria.[40,47] Para lograr la activación de los linfocitos T frente a antígenos del oído interno se han utilizado tanto homogeneizados del mismo[48,49] como péptidos específicos como la coclina, expresada abundantemente en el oído interno, o la β-tectorina.[50-52] Esto se conoce como el modelo de laberintitis experimental por transferencia de linfocitos T activados.

2.4. Diagnóstico Diferencial

Debe establecerse el diagnóstico diferencial con la hipoacusia súbita, la enfermedad de Menière, la otosífilis[53] el neurinoma acústico, y ocasionalmente con alteraciones neurológicas y oncológicas que cuando afectan a la duramadre pueden manifestarse como una hipoacusia neurosensorial rápidamente progresiva como son la meningitis, la esclerosis múltiple, metástasis y el linfoma. Otros ejemplos involucran a la sordera neurosensorial no sindrómica autosómica dominante DFNA-16, que aparece en personas jóvenes y responde a glucocorticoides[54,55] o el síndrome de Muckle-Wells que también tiene un origen genético y que presenta un cuadro clínico similar al de algunas enfermedades autoinmunes sistémicas, pero sin respuesta a los corticoesteroides.[56-59]

La disfunción del oído interno se conoce que puede estar asociada con numerosas enfermedades autoinmunes. El prototipo de enfermedad autoinmune que conduce a lesión en el oído interno es el Síndrome de Cogan que está constituido por una hipoacusia neurosensorial, vértigo, acufenos y una queratitis intersticial no sifilítica. Por otro lado, tenemos el síndrome de Vogt-Koyanagi-Harada que además incluye una meningitis aséptica, despigmentación de la piel alrededor de las pestañas y pérdida de las mismas. Podemos encontrarnos también con una disfunción cocleovestibular en el Lupus Eritematoso Sistémico (LES), la enfermedad de Behçet, el síndrome de Sjögren, la granulomatosis de Wegener, el síndrome de Susac o la tiroiditis de Hashimoto.[60]

Enfermedades sistémicas asociadas a la EIOI						
Anemia hemolítica autoinmune y perniciosa	Cirrosis Biliar 1ria	DM tipo 1	Enfermedad de Addison	Granulomatosis de Wegener	Pénfigo vulgar	Síndrome de anticuerpos antifosfolípidos
Arteritis temporal	Colitis ulcerosa	Dermato-miositis	Enfermedad de Behcet	Hepatitis autoinmune	Penfigoide ampolloso	Síndrome de Good-Pasture
Artritis reumatoide			Enfermedad. de Graves	Lupus Eritematoso Sistémico	Policondritis recidivante	Síndrome de Guillain-Barre
			Enfermedad de Hashimoto	Miastenia Gravis	Polimiositis	Síndrome de Sjogren
			Esclerosis múltiple		Púrpura Trombocitopénica idiopática	
			Espondilitis anquilosante			
			Encefalomielitis Aguda Diseminada			

Tabla 4: Enfermedades sistémicas asociadas a la EIOI.

2.4.1. EIOI en las enfermedades autoinmunes sistémicas

En algunos pacientes la hipoacusia neurosensorial es el primer síntoma de una enfermedad autoinmune sistémica. En estos casos la aparición de otros síntomas, así como la presencia de autoanticuerpos como factor reumatoide

(FR), anticuerpos antinucleares (ANAs), anticuerpos anticitoplasma de neutrófilo (ANCAs), anticuerpos anticélulas endoteliales (AECAs), antifosfolípidos, antitiroglobulina, antiperoxidasa, etc., nos pueden orientar en el diagnóstico.

En pacientes con artritis reumatoide (AR) o con LES se ha demostrado una hipoacusia neurosensorial en el 70%, cuando se estudia la audición mediante audiometría de altas frecuencias, y esta pérdida auditiva se correlaciona con la presencia de anticuerpos anticardiolipina y crioglobulinas séricas.[61,62]

3. HIPÓTESIS Y OBJETIVOS

3.1 HIPÓTESIS

Dado que el PET y la RM se han mostrado eficaces para el diagnóstico y evaluación de procesos autoinmunes resaltando zonas con actividad inflamatoria especifica en estas enfermedades, podrían ser también una herramienta de utilidad para la enfermedad inmunomediada del oído interno.

3.2. OBJETIVOS

3.2.1. Objetivo principal

Evaluar el rol de la RM con Gd intratimpánico y el PET para la caracterización de la EIOI primaria o secundaria y la posible inclusión de ambas herramientas en el algoritmo diagnóstico.

3.2.2. Objetivos secundarios

1.- Demostrar la presencia de hídrops endolinfático en pacientes afectos por EIOI.

2.- Comprobar si existen diferencias respecto al hallazgo de hídrops endolinfático entre la enfermedad primaria y secundaria.

3.- Analizar el rendimiento del PET para evaluar la actividad que ocurre en los distintos órganos de pacientes con EIOI, especialmente en aquellos con ausencia de autoanticuerpos.

4.- Correlacionar la actividad en el PET con la clínica.

4. MATERIAL Y MÉTODOS

4.1 Diseño

Estudio unicéntrico, retrospectivo y observacional de todos los pacientes con sospecha diagnóstica de hipoacusia inmunomediada en el HUPHM desde el enero del año 2014 hasta diciembre del año 2016.

4.2 Lugar de realización del estudio

El Hospital Universitario Puerta de Hierro-Majadahonda (HUPH) es un centro hospitalario de titularidad pública, perteneciente al Sistema Nacional de Salud, afiliado a la Universidad Autónoma de Madrid, situado en Majadahonda, en el Noroeste de Madrid.

Es el hospital de referencia de atención especializada del "Área 6 de Salud" de la Comunidad de Madrid. Proporciona asistencia sanitaria a una población de más de 550.000 habitantes del Noroeste de la comunidad.

4.3. Pacientes

Este estudió incluyó a 67 pacientes con sospecha de una enfermedad inmunomediada del oído interno (47 mujeres y 20 varones con un rango de edad entre los 15-72 años) reclutados en el HUPH desde enero de 2014 hasta diciembre de 2016.

Este estudio fue aprobado por el comité local de ética e investigación (PI 148-14, Acta 306, 12-01-2015 y PI 15/16, Acta 04.16). Se obtuvo un consentimiento informado para la participación en el estudio de cada uno de los pacientes.

4.3.1 Criterios de inclusión:

Los criterios primarios de inclusión incluyeron a los pacientes con:

Sospecha de EIOI teniendo en cuenta uno de los 4 subtipos de EIOI:

1. Hipoacusia bilateral asimétrica y progresiva (semanas a meses) (HNSP)
2. Hipoacusia neurosensorial súbita; más de dos episodios al año (horas a días) (HNSS-R)
3. Hipoacusia fluctuante unilateral secundaria a una afectación contralateral (meses a años) (HNSF)
4. Enfermedad de Menière Inmunomediada (bilateral)

- Todos respondieron a tratamiento con corticoesteroides y/o agentes inmunosupresores.
- Todos eran mayores de 15 años (los menores de 18 años acudieron con sus tutores legales los cuales firmaron el consentimiento informado en su nombre).
- Todos debían contar con un estado mental saludable y con la capacidad de entender el estudio y acudir a las consultas de seguimiento pudiendo responder a las pruebas audiológicas y cuestionarios de evolución que serian efectuados.

4.3.2. Criterios de exclusión:

Los criterios de exclusión fueron los siguientes:

- Otras causas no-inmunomediadas de hipoacusia como el trauma acústico, la ototoxicidad o la hipoacusia congénita fueron descartadas.
- Los pacientes que estuvieran tomando medicación que pudiese interactuar con medios de contraste con gadolinio (quimioterápicos y medicación antirretroviral)
- Antecedentes de reacciones alérgicas a medios de contraste.
- Por otro lado: secuelas otorreicas activas, insuficiencia renal, portadores de marcapasos u otros cuerpos extraños metálicos.

4.4. Historia clínica y Exploración ORL

La historia médica de cada paciente fue documentada. Un examen otorrinolaringológico fue realizado, así como una evaluación audiológica completa incluyendo visión directa otomicroscópica e impedanciometría.

4.5 Métodos audiológicos

Los niveles auditivos fueron evaluados con una audiometría tonal liminar. Los umbrales de tonos puros (125- 8000Hz) fueron medidos con un audiómetro manual (Madsen Orbiter 922, versión 2; Madsen Electronics, Taastrup, Denmark) equipado con unos cascos TDH-39 supra-aurales (Telephonics Co., Farmingdale, NY, USA). La hipoacusia ha sido considerada como una pérdida promedio de más de 30dB (500 + 1000 + 2000 + 4000 Hz). El promedio

esperado del rango de tonos puros audiométricos para sujetos normales está publicado en el ISO 7029 (International Organization for Standardization, 2000).

La audiometría de altas frecuencias (AAF) que abarca frecuencias desde 8 a 20KHz sólo explora la vía aérea. La AAF permite evaluar la porción más basal de la cóclea, siendo esta la zona coclear más frágil permitiendo así detectar alteraciones auditivas de forma más precoz.[63]

La AAF (9000 -20000 Hz) fue realizada con el mismo audiómetro y unos audífonos Koss HV/1A circumaurales. Todo el material audiométrico fue calibrado de acuerdo a las recomendaciones de sus fabricantes, así como de los estándares ISO 389-112 y IEC 60645-113. Los transductores fueron calibrados de acuerdo a los estándares ISO 389-112.

Esta modalidad de audiometría no se usa de forma habitual en la exploración instrumental de la audición, entre otras razones porque aumenta el tiempo de realización y hasta la actualidad no se había encontrado justificación en el empleo de esta prueba audiométrica en la rutina clínica diaria.

La utilidad de la AAF en el diagnóstico subclínico de la hipoacusia, aunque el paciente no perciba subjetivamente la pérdida, está comprobada ya que estas frecuencias son las primeras en afectarse cuando se lesiona el oído interno.[63-65]

Por este motivo, la utilización de esta prueba desde la sospecha de una enfermedad autoinmune o reumática, nos puede informar del comienzo de la hipoacusia y con ello ampliar nuestras posibilidades de tratamiento precoz y prevención.

Patrones audiométricos conocidos: *(ASHA: American Speech-Language-Hearing Association)*[66]

1º.- Normal: existe una superposición de vía ósea y la vía aérea, por encima del umbral de 25 dB.

2º.- Hipoacusia neurosensorial o de percepción: ambas vías con el mismo umbral, pero con pérdida igual o mayor a 25 dB.

3º.- Hipoacusia de transmisión o conductiva: una vía ósea normal con una vía aérea patológica, no mayor de 60db. Se denomina "Gap" la distancia entre ambas curvas.

4º.- Hipoacusia mixta: combinación entre los dos tipos de hipoacusia descritos anteriormente. Existe un "Gap", que desaparece en las frecuencias agudas, cuando la pérdida es mayor de 60db.

Se suele clasificar según el rango de frecuencias afectado teniendo en cuenta las frecuencias bajas, medias y altas. Teniendo en cuenta que denominamos infrasonidos a las ondas acústicas inferiores a los 20 Hz, se consideran bajas frecuencias las que se encuentran entre los 20 y los 400 Hz, frecuencias medias o intermedias las que estén entre los 400 y 1.600 Hz y altas aquellas frecuencias entre los 1.600 y los 20.000 Hz. Todas las frecuencias superiores a

20.000 Hz se llaman ultrasonidos.

Grados de hipoacusia: [66,67]

Según su intensidad, la hipoacusia se clasifica en:

- Leve: cuando existe una pérdida entre 26 y 40 dB
- Moderada cuando existe una pérdida entre 41 y 70 dB
- Severa cuando existe una pérdida entre 71-90 dB

- Profunda o cofosis pérdida superior a 90 dB

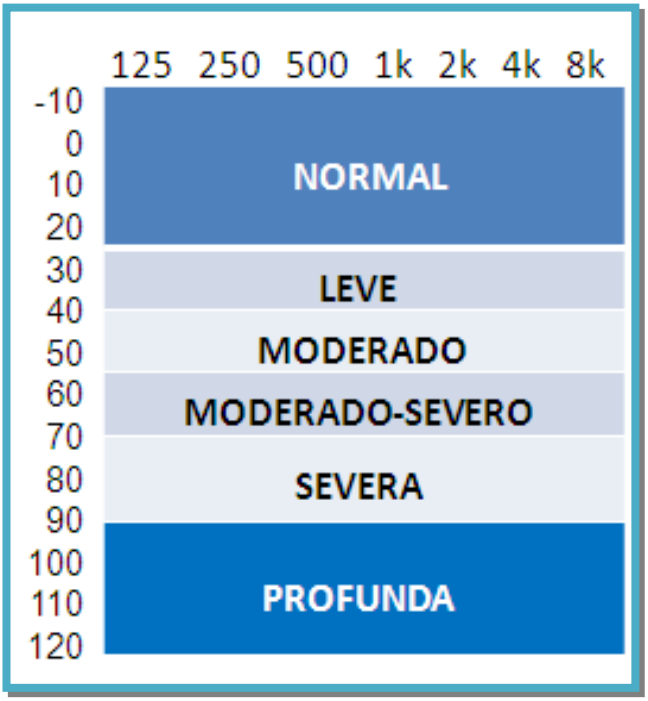

Figura 2. Audiograma mostrando los rangos de hipoacusia. Basado en el ANSI "American National Standards Institute"; dB Decibelios (-10 a 120); Frecuencia (125-8K).

4.6 Análisis Estadístico:

Se realizó un análisis descriptivo de las variables categóricas mediante frecuencias absolutas y relativas; y en las variables numéricas, mediante la media y desviación estándar o mediana y percentiles 25 y 75, según cumplimiento de la asunción de normalidad, así como los valores mínimo y máximo.

El análisis univariante se llevó a cabo con la prueba U Mann-Whitney para contrastar variables numéricas y prueba de Chi-cuadrado o estadístico exacto de Fisher para contraste de hipótesis de variables categóricas, según proceda.

El nivel de significación se ha establecido en 0,05. El software utilizado ha sido Stata v 14.1 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.)

4.7 Métodos de estudio y variables

4.7.1 RM con gadolinio intratimpánico

Todos los pacientes recibieron 0.45-0.9 ml de una solución de contraste intratimpánica (Ácido Gadotérico, un medio de contraste con base de gadolinio. Dotarem® 0.5 mmol/ml solución inyectable, Guerbet, Aulnaysous- Bois, France) con una concentración de 1/8 (1 ml gadolinio en 7 ml de suero) bilateralmente, previa anestesia del canal timpánico y de la membrana timpánica. Este método fue descrito previamente y aplicado en el HUPH (comité ético de investigación clínica, CEIC, del hospital PI 148-14, Acta 306, 12-01-2015)[3,68,69]

La exploración fue realizada 24-28 horas después en un equipo Philips ACHIEVA 3 T (Best, Holanda) con antena SENSE de ocho canales y una secuencia 3 D real IR con tiempo de repetición de 6000 ms, tiempo de eco de 107 ms, tiempo de inversión de 1650 ms, ángulo de inversión de 180◦, NSA 1, factor SENSE 1,5 ×1, campo de visión de 160×160×18 mm, tamaño de vóxel 0,55×0,63×1 mm/píxel. La secuencia se realizó en el plano axial y su duración fue de 12,42 minutos.

Sin conocer los datos clínicos de cada paciente (estudio ciego) dos neurorradiólogos con 6 a 15 años de experiencia analizaron los datos de cada imagen. Como referencia anatómica para medir el hídrops vestibular se eligió el plano axial del vestíbulo, que incluye la práctica totalidad del canal semicircular lateral. Para valorar el hídrops coclear se empleó la proyección axial centrada en el plano medio del modiolo que permitiera visualizar todas las vueltas de la cóclea y la rampa coclear en el centro. Estas referencias anatómicas ayudaron a establecer los grados según un esquema conocido (los criterios de Barath).[3,70,71] El gadolinio inyectado en el oído medio 24 horas antes de la

evaluación con RM permitió un contraste de imagen adecuado y fue bien tolerado por la mayoría de los pacientes causando únicamente molestias leves de corta duración en algunos.

De acuerdo a los criterios de Barath[71] el grado I de hídrops coclear fue definido como una dilatación muy leve de un conductor coclear no visible exceptuando pequeñas partes que resaltan de la perilinfa de la rampa vestibular. El grado I vestibular presenta una distensión del espacio endolinfático del sáculo, utrículo o ambos con el espacio perilinfático todavía visible a lo largo de la periferia del laberinto óseo. En el grado II coclear la escala vestibular está obstruida de manera uniforme por la distención del acueducto coclear y en el grado II vestibular el laberinto óseo está completamente rodeado o incluido por la dilatación de los espacios endolinfáticos.

La presencia de vértigo, tinnitus, mareo y presión ótica fueron descritas. Enfermedades sistémicas como el Wegener, tiroiditis autoinmune, enfermedad de Sjögren, colon irritable, síndrome de Cogan, síndrome de Raynaud, LES, Hemocromatosis, síndrome antifosfolípidos, esófago de Barret y la encefalitis autoinmune fueron algunos de los diagnósticos que acompañaban a estos pacientes.

4.7.2. PET-TAC

Un PET (con 18F-FDG) fue realizado para evaluar implicación sistémica, así como actividad en la región del oído interno. La interpretación de las imágenes de PET fue hecha por dos médicos nucleares que desconocían la historia clínica. Antes de la realización de la prueba, la glucemia fue medida en todos los pacientes y ninguno tenía hiperglicemia o diabetes mellitus.

Estas imágenes se obtuvieron utilizando un sistema PET (Biograph 6, Siemens Medical Systems, Knoxville, TN, USA). Seis horas de ayuno antes de la realización de la prueba fueron requeridas por parte de los pacientes. El registro de las imágenes se inició 60 minutos después de la inyección intravenosa de 370 MBq de 18F-FDG. El protocolo de imágenes incluía una imagen base selectiva de la base del cráneo (10 minutos/BED) seguida por un estudio PET estándar de todo el cuerpo (4 minutes/BED). Este proceso fue aprobado por el comité de ética e investigación del HUPH (PI 15/16, Acta 04.16). Las imágenes fueron reconstruidas con una matriz de 168x168 utilizando un algoritmo ordenado de subsecuencia máxima de reconstrucción.[16]

4.7.3. RESPUESTA AL TRATAMIENTO

En relación con la respuesta al tratamiento, fue considerado completo cuando los umbrales auditivos fueron clasificados como normales de acuerdo al ISO 7029 (International Organization for Standardization, 2000). Se consideró una respuesta parcial cuando el incremento en los umbrales fue demostrado en un seguimiento post-tratamiento con ATL (siendo la hipoacusia considerada previamente como una pérdida promedio de más de 30 dB en 500 + 1000 + 2000 + 4000 Hz). Una respuesta nula fue interpretada cuando no se observa respuesta alguna en el seguimiento con ATL.

5. RESULTADOS

Un total de 67 pacientes (47 (70,15%) mujeres y 20 (29,75%) hombres) con sospecha de EIOI fueron estudiados. Fueron clasificados según tuviesen una EIOI primaria o una EIOI secundaria. Un total de 38 pacientes presentaron una EIOI primaria y 29 una EIOI secundaria.

	Género (H/M)		RESPUESTA A ESTEROIDES				PET			RM con Gd IT		
	H	M	No Resp	Parcial	Completa	N/A	Normal	Patológico	No realizado	Normal	Patológica	No realizada
Primaria	18	19	4	10	22	1	7	10	20	5	11	22
Secundaria	2	28	4	7	14	5	6	7	17	9	2	18
Total	20	47	8	17	36	6	13	17	37	14	13	40

Tabla 5: Relación entre la EIOI primaria y secundaria con la respuesta a corticoides, los resultados del PET y de la RM con Gd IT.

Respecto a la forma de manifestación, 28 pacientes ~~a~~ presentaron una hipoacusia brusca y 39 indicaron que su hipoacusia fue fluctuante en el momento del diagnóstico. Se clasificaron dentro de los 4 subgrupos de EIOI mencionados anteriormente: A. Hipoacusia bilateral asimétrica y progresiva; B. Hipoacusia neurosensorial súbita; C. Hipoacusia fluctuante unilateral secundaria a una afectación contralateral y D. Enfermedad de Menière Inmunomediada. El grupo A contaba con 14 pacientes, el B con 14 pacientes, el C con 19 pacientes y el D con 20 pacientes.

Todos los pacientes fueron sometidos a una ATL y a una AAF. Los pacientes con una hipoacusia fluctuante incluyendo aquellos con una hipoacusia fluctuante unilateral secundaria a un proceso contralateral y a una enfermedad de Menière inmunomediada presentaron una evaluación clínica y subjetiva de su hipoacusia recurrente. La hipoacusia recurrente subjetiva ocurrió en un rango de 1 a 8 veces a partir del primer episodio hasta el momento del estudio. Sin embargo, la hipoacusia recurrente que fue clínicamente comprobada ocurrió en un rango menor, de 1 a 5 veces excepto en dos casos: un paciente varón con una EIOI primaria que presento 9 recurrencias y una paciente con una enfermedad de Menière con 7 recurrencias. De los 67 pacientes, 39 tenían una hipoacusia fluctuante en los cuales 80 recurrencias objetivas fueron registradas. De aquellos pacientes diagnosticados con una hipoacusia neurosensorial súbita inicialmente, 18 de 28 presentaron recurrencias clasificándose consecuentemente entre aquellos con hipoacusia fluctuante.

Dieciocho pacientes (26.8%) presentaron síntomas vestibulares en algún momento después del inicio de los síntomas y solo 11 pacientes (16,4 %) se quejaban de sensación de plenitud aural. Los acúfenos fueron el síntoma más frecuente ocurriendo en 38 (56,7%) pacientes de manera uni o bilateral.

Algunas enfermedades autoinmunes sistémicas fueron descritas entre los pacientes con una sospecha de EIOI secundaria.

Enfermedades Sistémicas	Varón	Mujer
Enfermedad inflamatoria intestinal		1
Síndrome de Wegener		1
Síndrome de Susac		1
Tiroiditis Autoinmune	1	13
Enfermedad del tejido conectivo		2
Síndrome de Sjögren		2
Vitiligo	1	
Síndrome de Raynaud		2
Policondritis recidivante		1
Síndrome de Cogan		1
Lupus Eritematoso Sistémico		1
Encefalitis autoinmune		1*
Fiebre Mediterránea familiar		1
Alergia al polen		1

Tabla 6: Relación entre las enfermedades sistémicas autoinmunes con respecto al género observando una clara propensión femenina

Otras asociaciones sistémicas no-autoinmunes incluyeron Hepatitis C, familiares en primer grado diagnosticados con Cirrosis biliar primaria y hemocromatosis. Un paciente presentaba una infección congénita por citomegalovirus asociada con una tiroiditis autoinmune. El paciente que

presentaba una encefalitis autoinmune tenía también diagnosticado un vitíligo y una tiroiditis autoinmune.

En todos los casos estudiados, las imágenes obtenidas mediante RM fueron válidas y de calidad suficiente para descartar la existencia de patología retrococlear, así como para evaluar el espacio endolinfático: 38 pacientes fueron sometidos a una RM del hueso temporal con previa inyección intravenosa de gadolinio (Gd IV) y 27 de ellos una RM del hueso temporal con previa inyección intratimpánica de gadolinio. De los 38 casos con Gd IV, 13 resultaron patológicos con distintas alteraciones como bucles de la arteria cerebelosa inferior, laberintitis osificante, quistes (uno aracnoideo y uno pineal) y una enfermedad isquémica de pequeño vaso. Con respecto a la RM con Gd IT, 13 de los 27 pacientes presentaron un hídrops endolinfático.

RM	Gd IV		Gd IT	
Normal	25	37,31%	14	20,90%
Patológica	13	19,40%	13	19,40%
No realizada	29	43,28%	40	59,70%
Total	**67**	**100%**	**67**	**100%**

Tabla 7: Hallazgos en la RM con Gadolinio intratimpánico vs con Gadolinio intravenoso.

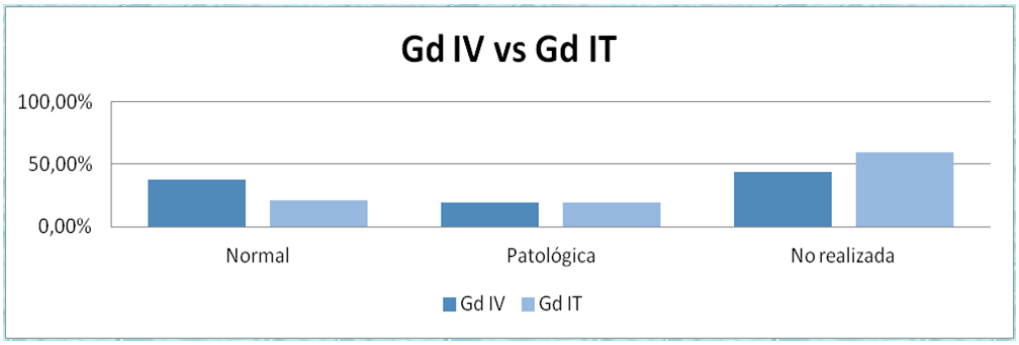

Figura 3: Comparación mediante grafica de los hallazgos en la RM con Gadolinio IT vs Gadolinio IV

Si consideramos el porcentaje de resultados específico de pacientes a los que se les realizo una RM con Gd IV vs Gd IT y no el global, la diferencia es aun más significativa encontrando un 34.21% alterado en una RM con Gd IV vs un 48,15% en una RM con Gd IT.

Un PET fue realizado en 30 pacientes y fue patológico en 17 de estos pacientes (7 con EIOI secundaria y 10 con EIOI primaria). Una mínima captación de FDG fue objetivada en el oído interno de 8 de estos pacientes. Sin embargo, no se observaron diferencias significativas que puedan establecerse entre la población normal y los pacientes con EIOI. Como se ha mencionado previamente, consideramos que no es adecuado tratar de cuantificar la actividad metabólica del oído interno basándonos principalmente.[72] Otros hallazgos relevantes consistieron en: 6 pacientes con captación en la glándula tiroides, una captación en la fosa nasal derecha y nasofaringe, dos nódulos pulmonares fueron identificados, un nódulo mamario derecho, dos captaciones en el arco aórtico, aorta ascendente y troncos supra aórticos, una captación en el útero y ovario izquierdo, uno en la aorta descendente y por ultimo una captación en las amígdalas palatinas y ganglios cervicales. Todos estos pacientes fueron estudiados a continuación de acuerdo a estos hallazgos confirmando en algunos de ellos que cursan con una EIOI secundaria.

PET-TC	EIOI Primaria		EIOI Secundaria	
Normal	7	18,92 %	6	20,0 %
Patológica	10	27,03 %	7	23,33 %
No realizada	20	54,05 %	17	56,67 %
Total	37	100 %	30	100 %

Tabla 8: Comparación de resultados en números totales y porcentajes de los hallazgos en el PET-TC en relación con la EIOI primaria y secundaria.

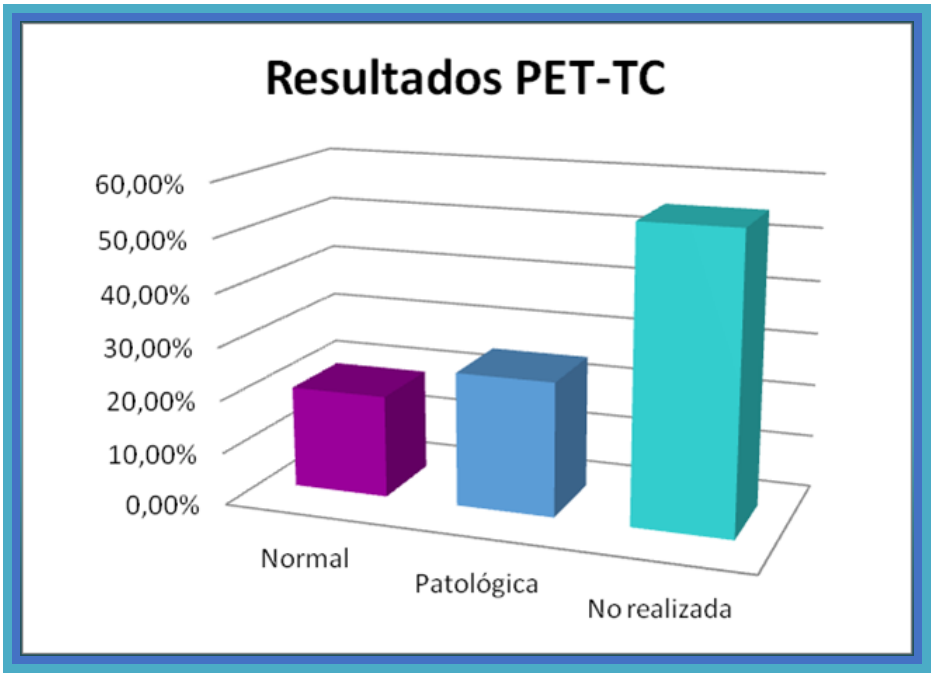

Figura 4: Resultados del PET TC medidos en porcentajes

Es importante destacar que en la Tabla 8 y en la Figura 4 aparecen unos porcentajes globales de resultados. Si descontásemos los casos no realizados, el porcentaje de casos alterados sería mucho mayor generando un impacto

muy superior en relación a los resultados del PET como prueba diagnóstica. Siendo así, estaríamos hablando de un 58.82% del total de PET-TC realizados los que se encontraron alterados en la EIOI primaria y 53.85% en la secundaria.

5.1 Tratamiento de la EIOI

El tratamiento inicial en nuestros pacientes incluyó varias opciones: solo corticoides intratimpánicos, corticoides intravenosos, corticoides orales o la combinación de dos o tres de estas opciones. Veintiocho (41,79%) pacientes recibieron como tratamiento inicial solo corticoides orales, seguidos por 10 (14,93%) los cuales recibieron la combinación de corticoides orales e intravenosos y 9 (13,43%) de ellos recibieron tratamiento con corticoides orales e IT. Nueve pacientes (13,43%) no recibieron ningún tratamiento inicial por rechazo fundado en los posibles efectos adversos del tratamiento y el “miedo” a recibir cualquier tratamiento corticoideo.

Las recurrencias fueron tratadas con las mismas combinaciones posibles: 19 (28,36%) de ellas recibieron tratamiento con corticoides orales e IT, y 11 (16,42%) solo corticoides IT. En este grupo, 2 pacientes fueron tratados con corticoides orales y Adalimumab en un caso y Azatioprina en el otro. Dos pacientes recibieron solo medicación inmunosupresora. En 21 pacientes (31,34%) no se produjeron recurrencias.

Tratamiento Inicial	Nº Pacientes	(%)	Tratamiento de Recurrencias	Nº Pacientes	(%)
CIT	6	8,96%	CIT	11	16,42%
CORTICOIDES IV	2	2,99%	CORTICOIDES IV	1	1,49%
CORTICOIDES ORALES	28	41,79%	CORTICOIDES ORALES	6	8,96%
CORTICOIDES ORALES + CIT	9	13,43%	CORTICOIDES ORALES + CIT	19	28,36%
CORTICOIDES ORALES + IV	10	14,93%	CORTICOIDES ORALES + IV	3	4,48%
CORTICOIDES ORALES + CIT + IV	1	1,49%	CORTICOIDES ORALES + CIT + IV	1	1,49%
CORTICOIDES ORALES + CIT + METOTREXATO	1	1,49%	CORTICOIDES ORALES + MEDICACION INMUNOSUPRESORA	2	2,99%
SIN TRATAMIENTO INICIAL	9	13,43%	SOLO MEDICACION INMUNOSUPRESORA	2	2,99%

Tabla 9: Distintas opciones de tratamiento inicial y de las recurrencias. Se documenta la cantidad de pacientes que han recibido cada tipo de tratamiento y el porcentaje respectivo.

La medicación inmunosupresora o inmunomoduladora utilizada incluyó medicamentos como el Metotrexato, Azatioprina, Rituximab y el Adalimumab. Una ATL y una AAF fueron hechas antes y después del tratamiento inmunosupresor para confirmar la respuesta al tratamiento.

5.1.1 Corticoides:

- Pauta de tratamiento

La dosis y la duración del tratamiento son claves para evitar la toxicidad por dicho fármaco. La pauta inicial más utilizada es de 60 mg o 1 mg/kg/día de prednisona o 6-metilprednisolona durante 1 mes, puesto que pautas más cortas o con dosis más bajas se han demostrado ineficaces y pueden llegar a aumentar el riesgo de recaída.[73]

La reducción de la dosis se debe realizar de forma gradual en el tiempo, teniendo en cuenta que debe ser aún más despacio si se ha mantenido el tratamiento con glucocorticoides a altas dosis durante más tiempo.

En las formas súbitas se administra en pauta descendente durante 4 semanas una dosis de 1 mg/kg/día de 6-metilprednisolona. En las formas rápidamente progresivas se utiliza durante 4 semanas una pauta de 1 mg/kg/día, manteniendo la dosis hasta lograr estabilidad en el audiograma y luego iniciar el descenso poco a poco hasta llegar a una dosis de mantenimiento de 10-20 mg/día durante otras 6 semanas**.**[74]

Figura 5: Esquema terapéutico basal en la sordera autoinmune

5.1.2. Tratamiento Intratimpánico

EL paciente se coloca en decúbito supino con el oído afectado angulado en dirección hacia el techo. Se limpia el conducto auditivo externo (CAE) y se visualiza la membrana timpánica bajo visión microscópica Anestesia local con lidocaína al 5% de manera tópica es aplicada a temperatura corporal rellenando el CAE y en completo contacto con la membrana timpánica. Una jeringa de tuberculina de 1-ml con una aguja espinal de 27-gauge ligeramente angulada para permitir una visualización adecuada del sitio de punción fue utilizada para inyectar una solución de 0,3-0,5 ml de 40 mg/ml de Metilprednisolona a través de la membrana timpánica en su cuadrante póstero-inferior. Se debe evitar puncionar el mismo sitio dos veces durante el curso del tratamiento.[74]

La inyección se administra lentamente para que la solución se concentre alrededor del nicho de la ventana redonda, rellenando completamente el oído medio dejando cualquier fluido restante en el CAE si precisa. Se le indica al paciente que debe evitar deglutir saliva, bostezar, hablar o modificar su posición actual durante 30 minutos para proveer una absorción máxima de la medicación a través de la ventana redonda evitando que drene a través de la trompa de Eustaquio. La dosis variaba en cada paciente sujeta a distintos factores específicos, sin embargo, casi siempre se aplicaron al menos 0,3 ml.

Algunos efectos adversos descritos en nuestros pacientes fueron dolor agudo de minutos a horas de duración, otros mareos y por último sensación de quemazón en la zona de aplicación de la inyección.

5.1.3 Metotrexato

Pauta de tratamiento:

La pauta de tratamiento más empleada es de 7,5 mg semanales, administrados en una única toma. En el tratamiento de ataque se usa la vía parenteral: subcutánea (SC), intramuscular (IM) o intravenosa (IV). Antes de iniciar el tratamiento, se aconseja realizar una radiografía de tórax y pruebas de serología frente al virus B y C de la hepatitis.

5.1.4 Azatioprina

Pauta de tratamiento:

La dosis inicial utilizada para la mayoría de las enfermedades es de 2-2,5 mg/kg/día por vía oral. Esta dosis deberá ser ajustada hasta un máximo de 5

mg / kg/ día según la respuesta clínica del paciente y su tolerancia hematológica.

5.1.5 Terapia Biológica

A los pacientes tratados con Adalimumab, se les administró mediante inyección subcutánea, 40 mg cada dos semanas de forma indefinida. La dosis se puede aumentar a 40 mg semanales si disminuye la respuesta.[75,76]

6. DISCUSIÓN

La enfermedad inmunomediada del oído interno puede presentarse como una afectación localizada cuando está restringida al oído interno únicamente o puede verse asociada a un desorden sistémico autoinmune siendo entonces cuando haremos referencia a esta como una EIOI secundaria. La EIOI secundaria incluye aproximadamente el 30% de los casos. Hughes sugirió que la hipoacusia podría iniciarse de manera abrupta, ser fluctuante a lo largo del tiempo y que podría asociarse a vértigo.[6,20]

La EIOI primaria es probablemente una enfermedad específica del oído interno de carácter autoinmune que involucra células T dirigidas a antígenos específicos del oído interno. Por otro lado, la EIOI secundaria puede ser consecuencia, evidenciada en el oído interno, de una irregularidad inmune sistémica. Los diagnósticos diferenciales que deben tenerse en consideración incluyen la enfermedad de Menière con afectación predominantemente coclear y una hipoacusia neurosensorial súbita la cual ahora se considera que está asociada a autoinmunidad en el 25% de los casos.[6,10,13,15,77-79]

En nuestra serie de casos, el 41,79% (28/67) de ellos debutan con una hipoacusia neurosensorial súbita, y el 58,21% (39/67) con una hipoacusia de carácter fluctuante.

La presencia de hídrops endolinfático fue confirmada en un subgrupo de pacientes con EIOI mediante las imágenes de RM tras la aplicación intratimpánica de gadolinio como herramienta diagnóstica. Este hallazgo corrobora algunos de los pocos estudios histopatológicos realizados previamente en pacientes con EIOI y eleva la sospecha del hídrops

endolinfático como un posible mecanismo inmunopatológico responsable en los pacientes en los que se encuentra dicho hallazgo.[80-82]

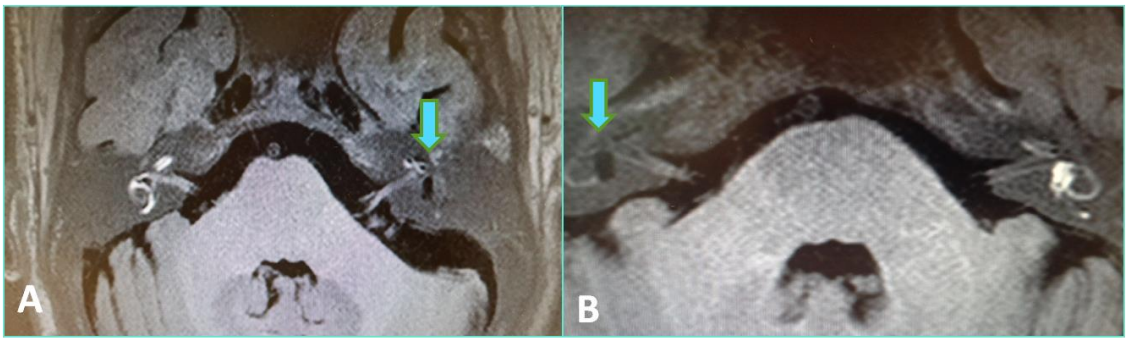

Figura 6: RM con Gadolinio intratimpánico de dos de nuestros pacientes mostrando en la primera imagen (A) un hídrops endolinfático a nivel de la cóclea y vestíbulo del oído izquierdo y en la segunda (B) en la cóclea y vestíbulo derechos. Secuencia axial 3D-IR.

La teoría del hídrops inmunomediado consiste en una respuesta inmune en el saco y conducto endolinfático generada por autoanticuerpos, inmunocomplejos, linfocitos T autorreactivos o lesión de los fibrocitos del ligamento espiral y/o de las células marginales de la estría vascular por el mismo mecanismo, con la consiguiente alteración del transporte de K y empeoramiento de la reabsorción de la endolinfa. Esto conlleva una dilatación del espacio endolinfático. Se ha objetivado en huesos temporales de pacientes con diagnostico de hídrops endolinfático la existencia de fibrosis perisacular, hipoplasia o atrofia del saco endolinfático, e incluso bloqueo óseo del acueducto vestibular.[17,47,79,82]

La mayor ventaja que le encontramos a la RM con gadolinio IT es que la interpretación de las imágenes es sencilla y requiere únicamente de un corto y rápido proceso de aprendizaje. Fue relativamente bien tolerada por la mayoría de los pacientes, con muy pocas complicaciones. No se observó en ningún caso un deterioro de la función auditiva tras la aplicación del Gd IT en estudios previos en pacientes o voluntarios sanos. Veinticinco pacientes tuvieron otalgia usualmente leve durante unas horas tras la aplicación del Gd IT.

El principal inconveniente de esta herramienta es la limitada disponibilidad para la administración intratimpánica y el tiempo extenso en la realización de la secuencia de imágenes lo cual lo hace más sensible a movimientos y resultados artefactados.[3] La administración intratimpánica, sin embargo, tiene la ventaja de necesitar una menor dosis de contraste. Usualmente con menos de 0,9 ml es suficiente teniendo un porcentaje muchísimo menor de toxicidad. El gadolinio aplicado en el oído medio 24-28 horas antes de la RM produjo un contraste de imágenes adecuado y fue relativamente bien tolerado por los pacientes.

La RM permite un acceso anatómico detallado al espacio endolinfático casi sobreponiéndose a una evaluación histológica directa. En varios estudios histológicos y radiológicos la presencia de hídrops endolinfático en varias patologías del oído interno ha sido demostrada. La demostración en RM de dicho hídrops puede ser de gran utilidad para el diagnóstico de varias enfermedades del oído interno que involucran síntomas como el vértigo y la hipoacusia fluctuante.[3,83] Con respecto a la RM con Gd IT en nuestros pacientes, 13 de los 27 pacientes presentaron un hídrops endolinfático coclear.

Se ha documentado que la combinación de una RM con imágenes de PET puede incrementar la sensibilidad de un algoritmo diagnóstico de patologías autoinmunes. El hídrops coclear es el observado mayoritariamente en pacientes con EIOI primaria. Se observa en primer lugar sobre todo en el sáculo, seguido por la cóclea, el utrículo y en último lugar por los canales semicirculares.[84,85]

La dificultad en el diagnostico de una EIOI primaria representa un reto para el otorrinolaringólogo. La utilización del PET nos permite certificar la ausencia de otros órganos afectados reforzando el diagnóstico de una EIOI primaria. La

EIOI también ha sido más fácil de confirmar mediante la aplicación de imágenes de PET. Se puede identificar cualquier anormalidad dada por hipo o hipermetabolismo de los oídos afectados. No obstante, la evaluación de la captación metabólica del oído interno es un desafío dado el volumen tan pequeño que representa el oído interno. Se ha comprobado la utilización y beneficio para el diagnóstico y seguimiento del PET en enfermedades neurológicas como son la epilepsia, encefalitis límbica, enfermedad de Alzheimer, enfermedad de Huntington, enfermedad de Parkinson entre otras.[87,88]

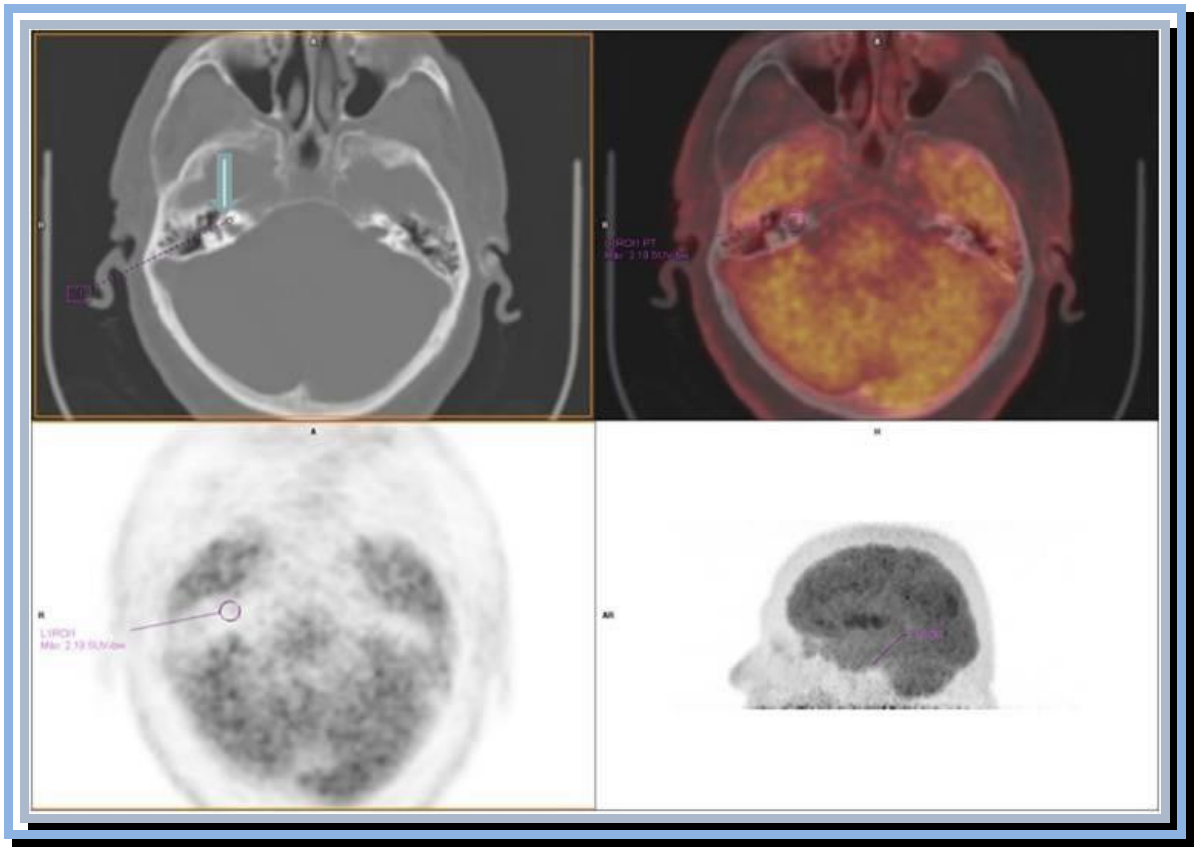

Figura 7: Captación de 18-FDG observada en el oído interno con un SUV de 2.19.

NOTA: El SUV describe el nivel de actividad que puede existir en lugar específico respecto a otras localizaciones. Una lectura del SUV = a 1 es considerada la línea de base o lo perteneciente a una actividad celular metabólica normal. Un SUV igual o superior a 2.5 puede estar indicando una metástasis, aunque cabe resaltar que otros factores también pueden provocar lecturas superiores a las normales.

Baumgartner et al.[86] realizó una evaluación mediante RM y PET de hallazgos en el SNC de pacientes con encefalitis límbica comparando los resultados con la presencia de ciertos tipos de autoanticuerpos. Dieciocho pacientes fueron analizados de los cuales a 12 se les realizaron las pruebas antes de la administración de tratamiento corticoideo, 3 habían recibido prednisona previamente, 2 plasma y 1 inmunoglobulina IV. Los hallazgos patológicos encontrados en la RM y en el PET no tuvieron diferencias estadísticamente significativas. Se encontró una asociación significativa entre el tipo de autoanticuerpo y los hallazgos del PET. El autoanticuerpo asociado fue el que se encuentra dirigido específicamente contra antígenos intracelulares. El mecanismo inflamatorio causa una hipercaptación de FDG apoyando la hipótesis de un mecanismo mediado por células T. Esta hipótesis es concordante con la de nuestro estudio.

Solo tres pacientes con EIOI secundaria presentaron un hídrops endolinfático en la RM. Uno de ellos tenía una infección congénita por citomegalovirus, otro una tiroiditis autoinmune y el último de ellos una polinosis. Cabe mencionar que en el caso de la infección por citomegalovirus puede haber confusión en el hecho de que la infección por si misma puede explicar el hidrops.[88]

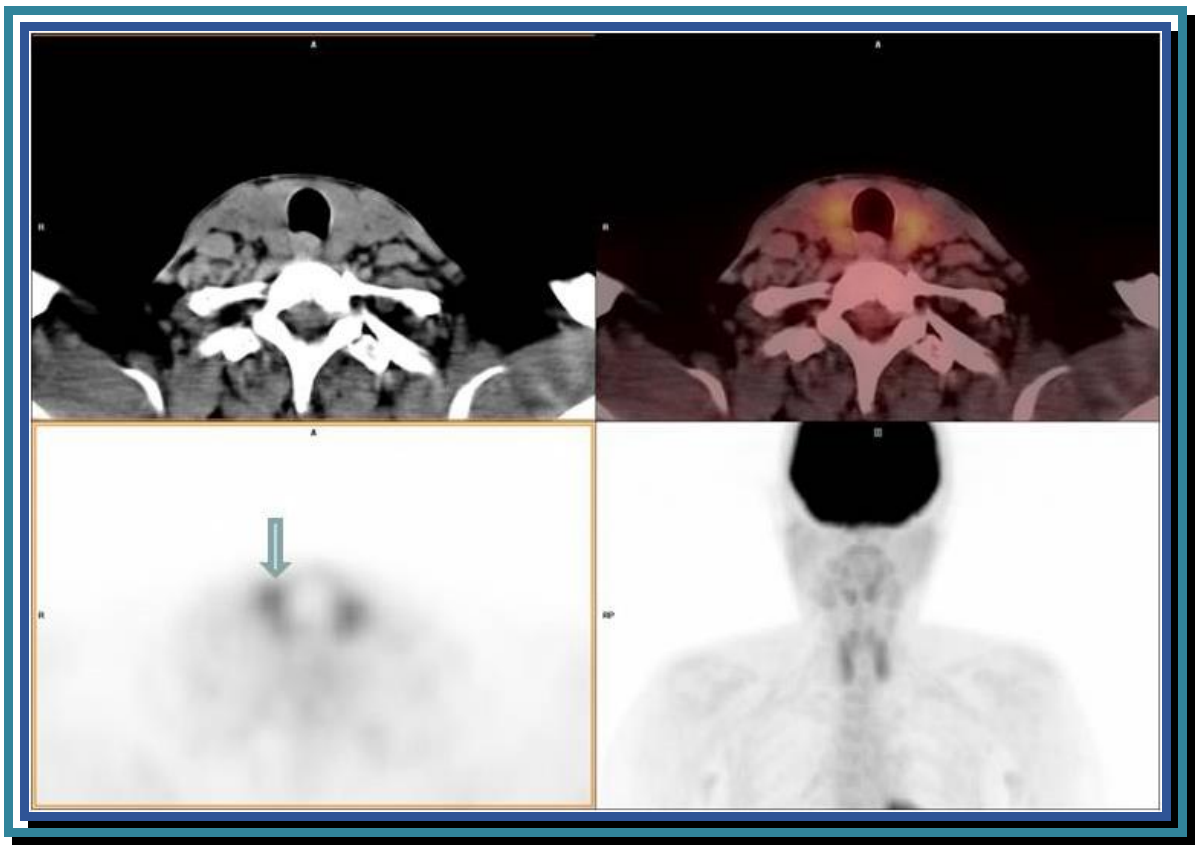

Figura 8: Captación tiroidea de 18-FDG en uno de los pacientes de nuestro estudio que había captado a su vez en el oído interno (Figura 7). Esta captación era desconocida y fue luego confirmada de origen autoinmune.

A pesar de que la sensibilidad diagnóstica puede mejorar por la combinación de estas dos pruebas, el diagnostico de la EIOI sigue estando hasta el momento, principalmente basado en las características clínicas y la respuesta al tratamiento, ya que aún no se ha descubierto un marcador inmunológico para la EIOI primaria a pesar de múltiples intentos realizados.[11,19]

Sin embargo, la aplicación de estas pruebas diagnósticas a un mayor número de pacientes facilitará el conocimiento de la EIOI y podrá permitir el seguimiento y control de esta entidad patológica del oído interno.

Desde la descripción de esta enfermedad el tratamiento más utilizado han sido los corticoides. Constituyen el “Gold Standard” en el tratamiento de la EIOI, por lo que cualquier otro tratamiento que se vaya a utilizar debe probar su eficacia respecto a los corticoides.[89,90]

Se considera una respuesta positiva al tratamiento una mejoría de 10 a 15 dB en al menos una o dos frecuencias en la audiometría tonal liminar, o del 10 al 20% en el reconocimiento de palabras. Otros criterios de respuesta para algunos autores serían la estabilización de la audición[91] o el control de las crisis vertiginosas a largo plazo.[92]

La toxicidad de los corticoides depende de la dosis y duración del tratamiento. Por ello, se intenta mantener al paciente con la dosis mínima efectiva y durante el periodo de tiempo más corto posible. La pauta inicial más utilizada es de 60 mg o 1 mg/kg/día de prednisona o 6-metilprednisolona durante 1 mes, ya que pautas más cortas o con dosis más bajas se han demostrado ineficaces y aumentan el riesgo de recaída.[72]

En las formas rápidamente progresivas se mantiene una pauta de 1 mg/kg/día durante 4 semanas, manteniendo la dosis hasta que el audiograma se estabiliza y disminuyendo la dosis paulatinamente a lo largo de 8 semanas hasta la dosis de mantenimiento de 10-20 mg/día durante otras 6 semanas. En las formas súbitas se administra 1 mg/kg/día de 6-metilprednisolona en pauta descendente durante 4 semanas.

En sorderas severas (pérdida mayor de 70 dB) se administran 3 pulsos de 500 mg y a continuación se aplica la pauta anterior La reducción de la dosis se realiza de forma gradual, más despacio si se ha mantenido el tratamiento con glucocorticoides a altas dosis durante más tiempo.

En ocasiones es conveniente añadir fármacos inmunomoduladores (Metotrexato, Azatioprina, anti-TNF, anti-IL I) al objeto de reducir progresivamente la dosis de corticoesteroides, contribuyendo también a la estabilización del cuadro clínico.[93]

En un metaanálisis se demostró que el Metotrexato no aportaba ningún beneficio frente al uso aislado de corticoides en el control de la audición.[95] Sin embargo, se logra una mejoría del vértigo o la inestabilidad en los pacientes que lo presentan, con tratamientos mantenidos a largo plazo.[92] Un estudio multicéntrico con Azatioprina demostró el control de la recurrencias permitiendo suprimir el tratamiento con corticoesteroides, con un seguimiento medio de 1 año.[93]

La tasa de respuesta global a los corticoesteroides es del 60%, y esta respuesta es muy variable: algunos pacientes mejoran sus umbrales de audición y la discriminación mientras que otros sólo mejoran en alguno de estos aspectos.[95]

Por otro lado, pacientes con fluctuaciones de la audición y progresión de la pérdida auditiva antes de recibir tratamiento, pueden mostrar después del tratamiento una estabilización de la audición sin obtener una mejoría de la misma.[91]

Además, aunque en la mayoría de los pacientes respondedores se logra disminuir la dosis de corticoides o incluso suprimirlos sin sufrir una recaída, en otros pacientes, especialmente niños[96] se puede presentar una pérdida auditiva dependiente de corticoesteroides.

La aplicación de corticoides intratimpánicos constituye un abordaje terapéutico muy tentador a tener en cuenta dado que es mínimamente invasivo y por su tipo de aplicación evita los efectos secundarios de los tratamientos sistémicos. No existe actualmente un consenso claro de la dosis exacta que se debe aplicar y cuanto debe durar el tratamiento ya que no existe un control pleno sobre la cantidad de medicación que llega al oído interno teniendo en cuenta la eliminación posible a través de la trompa de Eustaquio y la reabsorción parcial a nivel del oído medio. Esto conlleva a que su eficacia aún no ha sido totalmente determinada.[97] Actualmente se está estudiando la posibilidad de asociar distintos corticoesteroides a nanopartículas al objeto de que la penetración del fármaco sea mayor, utilizando una dosis menor y reduciendo la necesidad de repetir las inyecciones al conseguir una vida media más larga.[98]

Treinta y dos pacientes tuvieron una respuesta completa al tratamiento inicial con recuperación audiológica en todas las frecuencias y estando libre de síntomas. Nueve tuvieron una respuesta parcial al tratamiento inicial y 8 de ellos no tuvieron ningún tipo de mejoría.

Es destacable el hallazgo de HE en un subgrupo de pacientes afectos por EIOI primaria, puesto que no solo contribuye a esclarecer el sustrato histopatológico de esta enfermedad, sino que también ha demostrado una mejor respuesta al tratamiento con corticoesteroides, lo que le proporciona un valor pronóstico.

7. CONCLUSIONES

- La hipoacusia inmunomediada es una enfermedad de carácter progresivo que carece de un marcador serológico específico y evoluciona de manera diferente a otras enfermedades presentando periodos de inactividad intercalados con recaídas. La probabilidad de recaídas debe ser de conocimiento claro por parte del paciente una vez sea diagnosticada la enfermedad.

- Tanto el PET como la RM con Gd IT han demostrado la posibilidad de resaltar las zonas con actividad inflamatoria específica en estas enfermedades. No obstante, la evaluación de la captación metabólica del oído interno es un desafío dado el volumen tan pequeño que representa el oído interno.

- La utilización del PET nos permite certificar la ausencia de otros órganos afectados reforzando el diagnóstico de una EIOI primaria, así como diagnosticar enfermedad secundaria con autoanticuerpos negativos como el síndrome de Cogan.

- La presencia de hídrops endolinfático fue confirmada en un subgrupo de pacientes con EIOI mediante las imágenes de RM tras la aplicación intratimpánica de gadolinio como herramienta diagnóstica. El hídrops coclear es el observado mayoritariamente en pacientes con EIOI primaria. Este hallazgo se correlacionó con una mejor respuesta al tratamiento esteroideo.

- Siendo la EIOI una patología inusual, los resultados que provee nuestro estudio pueden ayudar a guiar futuros estudios y apoyar los estudios actuales disponibles para diagnosticar y tratar correctamente una EIOI primaria o secundaria.

- La disponibilidad de herramientas diagnósticas como RM y PET, nos ha permitido orientar la clasificación y caracterización de este tipo de hipoacusias, resultando especialmente útiles en la aplicación de un tratamiento adecuado y dirigido de forma individualizada.

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9. ANEXOS

Anexo 1:

“Examination of Hearing in a Rheumatoid Arthritis Population: Role of Extended-High-Frequency Audiometry in the Diagnosis of Subclinical Involvement.”

El objetivo de este estudio fue analizar los niveles de la audiometría de altas frecuencias en pacientes con artritis reumatoide y determinar a su vez, su asociación con los parámetros inmunológicos, hipoacusia y duración de la enfermedad. Se concluyó que la hipoacusia neurosensorial debe ser considerada dentro del contexto de la artritis reumatoide y se demostró que la audiometría de altas frecuencias es una herramienta útil a tener en cuenta para valorar un posible tratamiento modificador de la enfermedad o un tratamiento que pueda prevenir la pérdida auditiva.

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Research Article

Examination of Hearing in a Rheumatoid Arthritis Population: Role of Extended-High-Frequency Audiometry in the Diagnosis of Subclinical Involvement

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Objective. The aim of this study is to analyze the high-frequency hearing levels in patients with rheumatoid arthritis and to determine the relationship between hearing loss, disease duration, and immunological parameters. *Materials and Methods.* A descriptive cross-sectional study including fifty-three patients with rheumatoid arthritis was performed. The control group consisted of 71 age- and sex-matched patients from the study population (consecutively recruited in Madrid "Area 9," from January 2010 to February 2011). Both a pure tone audiometry and an extended-high-frequency audiometry were performed. *Results.* Extended-high-frequency audiometry diagnosed sensorineural hearing loss in 69.8% of the patients which exceeded the results obtained with pure tone audiometry (43% of the patients). This study found significant correlations in patients with sensorineural hearing loss related to age, sex, and serum anti-cardiolipin (aCL) antibody levels. *Conclusion.* Sensorineural hearing loss must be considered within the clinical context of rheumatoid arthritis. Our results demonstrated that an extended-high-frequency audiometry is a useful audiological test that must be performed within the diagnostic and follow-up testing of patients with rheumatoid arthritis, providing further insight into a disease-modifying treatment or a hearing loss preventive treatment.

1. Introduction

Autoimmune hearing loss was reported for the first time by McCabe in 1979. [1–3] A description of a series of patients with bilateral progressive sensorineural hearing loss (SNHL) and altered immunological tests in response to an immunosuppressive treatment was performed.

Rheumatoid arthritis (RA) is a connective tissue disease that has a disseminated erosive arthropathy associated with systemic manifestations. This immune-mediated disease may entail mainly SNHL [4–11], which is to occur in 25.2% to 60% [5, 9, 12–14] of the cases. The incidence of conductive hearing loss in RA is estimated at 4.8% to 14% [4, 14–20].

The pathogenesis of SNHL in RA still remains unclear, although it is potentially related to vasculitis [21], neuritis, ototoxicity [12, 21, 22], or an immunological disorder [13]. Several studies have attempted to demonstrate this pathogenesis due to the existence of specific antigens in the inner ear [7, 10, 12, 23, 24]. The pathogenesis of conductive hearing loss is also unknown, although a number of studies have proposed that it originates from a disorder in the incudostapedial joint [4, 14–20].

This study aimed to assess the real prevalence of SNHL in RA using advanced audiometric analysis based on extended-high-frequency audiometry (HFA), thus considering its effectiveness and clinical utility for inclusion in the routine diagnostic hearing tests. Furthermore, we analyzed the

immunological parameters to obtain an indicator of the inner ear impairment in these patients.

2. Materials and Methods

A cross-sectional descriptive study was carried out with comparative cases and controls matched for age and sex.

Inclusion Criteria. Fifty-three patients with RA (106 ears), both sexes, aged between 20 and 60, were diagnosed and treated in the office of the Rheumatology and Nephrology Departments of "Severo Ochoa" Hospital (Madrid, Spain). The diagnostic criteria and their respective scoring used for a definitive RA diagnosis were as follows: (A) joint involvement: 1 large joint = 0; 2–10 large joints = 1; 1–3 small joints (with or without involvement of large joints) = 2; 4–10 small joints (with or without involvement of large joints) = 3; >10 joints (at least 1 small joint) = 5; (B) serology (at least 1 test result is needed for classification): Negative Rheumatoid Factor (RF) and negative anti-citrullinated protein antibody (ACPA) = 0; low-positive RF or low-positive ACPA = 2; high-positive RF or high-positive ACPA = 3; (C) acute phase reactants (at least 1 test result is needed for classification): normal C-reactive protein (CRP) and normal Erythrocyte Sedimentation Rate (ESR) = 0; abnormal CRP or abnormal ESR = 1; (D) duration of symptoms: <6 weeks = 0; >6 weeks = 1. The classification criteria from the American College of Rheumatology (ACR) for RA (score-based algorithm: add score of categories A–D) consider that a score of > or = 6/10 is needed for classification of a patient as having a definitive RA.

Both a medical history and an ENT examination were performed, using the following *inclusion criteria*: patients who suffered from rheumatoid arthritis, both sexes, aged between 20 and 60.

Exclusion Criteria. Exclusion criteria are patients who suffered from another immune-mediated disease, inner ear disease, traumatic brain injury, Menière's disease, metabolic diseases, and cardiovascular disease, exposure to noise, and the use of ototoxic medication different from that used in the treatment of RA.

A control group of 71 patients (142 ears) was consecutively recruited in "Area 9" of Madrid, from January 2010 to February 2011.

The control group was composed of patients with a normal state of health, free from all signs or symptoms of ear disease and from obstructing wax in the ear canal, and with no history of exposure to noise, potentially ototoxic drugs, or familial hearing loss that attended our ENT department for head and neck or rhinologic disorders.

If the control population presented hearing thresholds in the limits of the normal range, according to the range of age and sex, assessed by pure tone audiometry (PTA) using frequencies of 125 to 8000 Hz, consequently an extended-high-frequency audiometry (HFA) of 8000 to 18000 Hz was also performed to determine the normal hearing parameters and use those parameters as references for the study.

A number of variables have been studied, such as demographic variables (age and sex), hearing variables (hearing thresholds with PTA and HFA), and variables related to the rheumatologic disease (activity, duration, and immunologic analysis). Disease activity is measured as active or nonactive.

2.1. Hearing Examination. The first otological test included an initial otoscopy and a hearing screening with PTA and HFA.

All the subjects suitable for inclusion were evaluated based on a questionnaire (Annex A in ISO 389-9: 2009) according to a written protocol based on ISO 389-9 recommendations on the determination of reference hearing threshold levels.

Audiometric tests were conducted by experienced audiometric technicians. For each test frequency, the signal was manually increased by steps of 5 dB until the test person responded, after which the signal was decreased by 10 dB and increased by 5 dB until response. The intensity to which the listener responded three out of five times was recorded as threshold (masking was used). The pure tone hearing thresholds (125–8000 Hz) were measured with a manual audiometer (Madsen Orbiter 922, version 2; Madsen Electronics, Taastrup, Denmark) and equipped with TDH-39 supra-aural earphones (Telephonics Co., Farmingdale, USA). Bone and air conduction audiometry were performed.

HFA thresholds (9, 10, 11.2, 12.5, 14, 16, and 18 kHz) were determined using a Madsen clinical audiometer (Madsen Orbiter 922, version 2; Madsen Electronics, Taastrup, Denmark) with a Sennheiser HDA 200 closed circumaural earphone (Sennheiser Co., Germany). All testing equipment for audiometry was calibrated according to ISO 389-5 (International Organization for Standardization, 2006) and the manufacturer's recommendations. The threshold was defined as the lowest decibel hearing level at which responses occurred in at least 50% of a series of ascending trials (ANSI, 2004) [26, 27].

The limit for the hearing loss to be considered was established when one or more frequencies have higher threshold than the frequency previously identified as normal in the control population [28].

2.2. Laboratory Analysis. An immunological analysis of all the parameters, including immunological RA activity (CRP and ESR), subgroup markers of RA (RF and antinuclear antibodies), acute phase reactants (APR), serum cryoglobulins, and anti-cardiolipin (aCL) and antithyroid antibodies, was performed.

2.3. Ethics. All the procedures used in this study and practiced on each patient were in agreement and regulated with approval from the "Severo Ochoa" Hospital (Madrid) Institutional Review Board and ethical code identified by the MINUTE: 11/09, 25/11/2009, IEC (Independent Ethics Committee) Internal code: 431-A (65/09), and the Declaration of Helsinki (1983). Informed consent was obtained from each participant. The same person performed all interviews. The subjects received no monetary compensation. Informed consent was obtained from all subjects, after being informed

of details about the purpose of the study, according to the recommendations from the Ethics Committee in our centre.

2.4. Statistical Analysis. Statistical analyses were performed using SPSS 15 (*Statistical Package for the Social Sciences*) for Windows. This study used quantitative and qualitative descriptive statistics, Chi-square test, Student's t-test, and Mann-Whitney U test. Logistic regression analysis was achieved by adjusting the estimate for some risk factors, including independent variables such as risk factors related to the patient, subjective hearing or rheumatic disease, with a dependent variable represented by the presence of sensorineural hearing loss. The estimate was established with 95% confidence intervals of the hearing loss prevalence in the PTA (threshold > 30 dB HL) and in the HFA (according to the hearing threshold of the control population for each frequency), adjusted for age (20–29, 30–39, 40–49, and 50–60 age ranges) and sex. A p value of <0.05 was considered significant.

3. Results and Discussion

The average age of the patients with RA was 50.5 years (interquartile range: 38–59 years), and the patients included 14 males and 39 females with a 26.4%/73.6% male/female ratio. The control population included 71 subjects (142 ears) belonging to Madrid Area 9; the patients were consecutively enrolled, with an average age of 38 years (20–60 years, 50 females and 21 males).

3.1. Pure Tone Audiometry. In this study, 43% of the study population with PTA had hearing loss (46 ears). The type of hearing loss was sensorineural, with high-frequency loss predominant. High frequencies were affected in 56.6%, medium frequencies in 17%, and low frequencies in 13.2% of the population. There was a significant difference in hearing thresholds (arithmetic mean) at 6000 Hz ($p = 0.001$) and 8000 Hz ($p = 0.001$) frequencies between patients with RA and the control population.

SNHL was bilateral and symmetric in 74% of the cases. There were no cases of conductive or mixed hearing loss. Our results showed that patients with RA had greater high-frequency loss than the control population (according to age range) (Figure 1). Regarding sex, there was a significant difference in the 4000 ($p = 0.038$), 6000 ($p = 0.004$), and 8000 Hz ($p = 0.009$) frequencies; there were lower auditory hearing thresholds in females compared to males. We observed that in patients with RA there was a statistically significant relationship between the hearing loss diagnosed by PTA and sex (OR = 3.46 (1.29–9.27)) and the age at which it was diagnosed (OR = 1.09 (1.04–1.15)).

3.2. Extended-High-Frequency Audiometry. A 69.8% prevalence of high-frequency SNHL in patients with RA was diagnosed using HFA. The arithmetic means of the hearing thresholds in patients with RA were compared with the controls and the result was a significant difference in all frequencies from 8000 to 18000 Hz ($p < 0.0001$) (Figure 2).

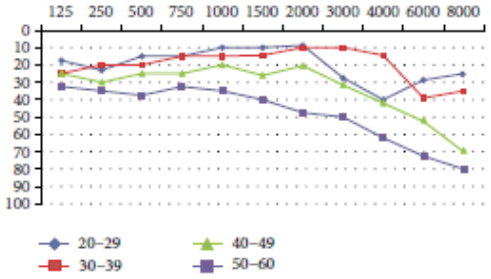

Figure 1: Hearing threshold with pure tone audiometry according to the age range of the study population with RA. Hearing thresholds < 30 dB: hearing normality values with PTA. Arithmetic means (y-axis: intensity, dB; x-axis: frequency, Hertz or Hz). RA: rheumatoid arthritis. PTA: pure tone audiometry.

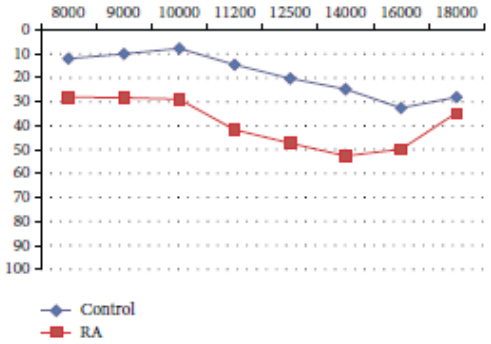

Figure 2: Hearing threshold with ultra high-frequency audiometry, without an age range, in both the control population and the study population with RA. Arithmetic means (y-axis: intensity, dB; x-axis: frequency, Hertz or Hz). RA: rheumatoid arthritis.

These results showed that hearing declined in patients with RA in all age ranges, which predominantly included 40-year-old and older patients (Figure 3).

Regarding sex, we obtained a significant difference between the means of the 8000 Hz ($p = 0.009$) and the 10000 Hz ($p = 0.026$) threshold frequencies, between male and female patients with RA, which demonstrated a greater hearing loss in males than in females.

3.2.1. Immunological Study. Regarding the characteristics of the study population, we observed that patients with RA showed a significant relationship between the SNHL measured with HFA and the aCL positivity (OR = 0.38 (0.15–0.94)).

3.2.2. Comparison between PTA and HFA. The diagnosis of SNHL in RA reached 69.8% with HFA and 43.4% with PTA. The chance of diagnosing hearing loss with HFA is 33.6 times higher compared to PTA OR = 29 (4.8–1184.43).

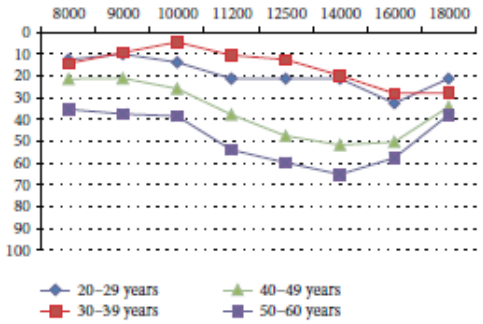

Figure 3: Hearing threshold with ultra high-frequency audiometry, within the age range of the study population with RA. Arithmetic means (y-axis: intensity, dB; x-axis: frequency, Hertz or Hz). RA: rheumatoid arthritis.

Table 1: Comparative analysis of results of SNHL and CHL as diagnosed using PTA in patients with RA, according to the reviewed sources. SNHL: sensorineural hearing loss; CHL: conductive hearing loss; PTA: pure tone audiometry; RA: rheumatoid arthritis.

Authors	Number of patients	% SNHL (PTA)	% CHL (PTA)
Our study	53	43.4	—
Magaro et al. [5]	20	55	—
Kastanioudakjs et al. [12]	45	35.5	—
Raut et al. [7]	35	60	—
Özcan et al. [8]	37	35.1	24.3
Takatsu et al. [10]	37	36.1	—
Bhama et al. [9]	25	60	12
Halligan et al. [13]	29	40	10
Murdin et al. [14]	55	29.6	1.9
Dikici et al. [21]	20	45	—
Baradaranfar and Doosti [32]	50	60	—

RA may cause SNHL [29], similar to other autoimmune diseases [13, 30]. Although the etiology of SNHL in RA is unknown, there have been a number of physiopathological hypotheses, such as the presence of vasculitis, neuritis, or immune-complexes that deposit in the inner ear or the effect of the possible ototoxic treatment used in the treatment of RA [5, 7, 12, 21, 22, 25].

Nevertheless, nowadays the treatment used in RA includes immune-modulating drugs that could control the progression of the SNHL in some patients. Thereby an early diagnosis of a possible subclinical SNHL by means of HFA (detected just before treatment is applied or along a possible long-term treatment such as chemotherapy) in order to allow a prior treatment (transtympanic or systemic corticosteroids) is of paramount importance.

(1) PTA in RA. The prevalence of SNHL with PTA in our study (43.4%) is within the same range as described in previous literature, which has been estimated between 25.2 to 60% [7, 8, 12, 13]. Unlike other studies, we did not observe conductive or mixed hearing loss in our study population (Table 1). Regarding the frequency affected, we obtained results that were consistent with several previous studies regarding the damage caused in high frequencies in patients with RA [5, 8, 10, 17, 31, 32]. Nevertheless, our results differed from those in studies performed by Raut et al. [7], who claimed a greater hearing loss in intermediate frequencies of 500 Hz, 1000 Hz, and 2000 Hz, and from Murdin et al. [14], who reported that patients mainly had hearing loss in low and medium frequencies (from 250 to 4000 Hz). Murdin proposed that the damage caused in low frequencies may be due to the association between RA and endolymphatic hydrops (caused by immune-complex deposits), which initially affects low frequencies and subsequently affects the high frequencies.

A comparison between the study and control groups using PTA revealed a significant hearing loss in patients with RA at frequencies of 6000 and 8000 Hz. Our results differ from other authors, who did not find significant differences between the two populations [12, 13].

Moreover, 73.9% of our patients with RA had bilateral, symmetric SNHL, which was a slightly lower result compared to the results obtained by Özcan et al.: 84.6% with bilateral SNHL [8] although these were clearly higher compared to the findings obtained in other studies [7, 12, 21]. In our study we observed a significant relationship between SNHL (diagnosed using PTA) and age (OR > 1), with a higher risk of developing hearing loss for patients over 40 years of age. In patients older than 50 and who only had unilateral SNHL the hearing thresholds using PTA became worse along the years, similar to findings reported by Halligan's studies [13]. However, studies performed by author did not show a correlation between SNHL and the age of the patient with RA [12, 21, 33].

In our study, we observed a significant relationship between SNHL and sex (OR > 1) with males demonstrating a higher risk of hearing loss and significant differences in high frequencies at approximately 4000, 6000, and 8000 Hz. These findings were consistent with those observed by Dikici et al. [21]. This hearing loss was not related to the greater exposure to noise in males in their working environment, which was an excluding factor in our study.

The persistent findings of high-frequency thresholds in female subjects might be explained due to the fact that the female ear canal has smaller average length and volume. Nevertheless, there could be other explanations for the gender difference, such as differences in exposure to workplace or extracurricular activity noise or different hearing levels as a result of a different phylogenetic origin. Moreover, the aging process may be different in males and females. There are many health factors that influence hearing status (smoking, hypertension, and diabetes) which may also influence the differences observed between males and females [26].

(2) HFA in RA. In most of the studies, the hearing loss diagnosis in patients with RA was performed using pure tone audiometry. In few studies a hearing screening was performed using frequencies higher than 8000 Hz [14, 21, 34, 35]. The usefulness of extended-high-frequency audiometry

in subclinical diagnosis of hearing loss has been proven [21, 35] and, for this reason, the use of this test from the beginning of the rheumatic disease can provide information on the development of hearing loss, thereby increasing the possibilities of early treatment and prevention.

Furthermore, 69.8% of our patients with RA were diagnosed with SNHL using HFA, which is a higher percentage compared to those obtained using PTA. Some studies showed that there were no references regarding the index of SNHL using HFA, because previous results were global (125–16000 Hz) [21, 36].

Our results do not show a significant correlation between SNHL diagnosed using HFA and age. This finding takes into consideration that normal age-related hearing loss in patients older than 50 from the control population is expected to have higher thresholds than those with RA since hearing loss is generally observed since early stages of the disease [21]. Regarding sex, our findings were consistent with those obtained by Dikici et al. [21] in which a greater hearing loss was observed in males, with significant differences in high-pitched frequencies of 8000 Hz and 10000 Hz.

In our study there were statistically significant differences in all of the frequencies studied between the hearing threshold in both the control population and patients with RA. The hearing loss is greater starting at 40 years of age with thresholds higher than 60 dB.

Öztürk et al. obtained similar results and found significant differences between the control population and the patients with RA, from a frequency 220 to 16000 Hz [36]. In our study, there were minimal hearing changes at 18000 Hz compared to controls. We are not able to compare these results with other studies because a frequency of 18000 Hz was not assessed. Normal age-related hearing loss in patients older than 50 from the control population is expected to have higher thresholds than those with RA since hearing loss is generally observed since early stages of the disease [21].

We found no correlation between SNHL diagnosed using PTA and HFA and the duration of the disease, which was consistent with other studies [12, 14, 32, 33]. However, we did obtain a correlation with the rheumatic disease activity in patients with RA and SNHL, similar to other authors [5, 12, 14, 31, 37]. These parameters were, as mentioned above, immunological RA activity (CRP and ESR), subgroup markers of RA (RF and antinuclear antibodies), acute phase reactants (APR), serum cryoglobulins, and anti-cardiolipin (aCL) and antithyroid antibodies.

The analysis of immunological parameters using specific laboratory tests was performed without obtaining conclusive results [5, 11, 23, 38, 39]. A statistically significant relationship ($p = 0.029$) between SNHL diagnosed using HFA and anti-cardiolipin (aCL) positivity (OR < 1) was observed. This finding might be due to the potential for inner ear thrombosis to be developed, which is found to be associated with high levels of aCL (risk factor for SNHL). In our study, 43.3% of the patients with RA had aCL positivity, which may cause confusion since it is usually associated with SLE [40–42].

No correlation between positivity to anti-nuclear antibodies (ANA), rheumatoid factor (RF), Sjögren's syndrome (SS), aCL, ESR, and SNHL has been reported [5, 12, 14].

4. Conclusion

There was a higher rate of patients diagnosed with SNHL using HFA (with the study finding an SNHL prevalence of 69.8%) compared to studies previously reported. SNHL in RA was bilateral and predominantly symmetric, affecting mainly high frequencies. Males over 40 had a greater risk of suffering from SNHL.

There were more cases of subclinical hearing loss diagnosed using HFA compared to PTA. These results lead us to consider HFA as a necessary test to diagnose subclinical hearing loss in patients with RA. An early intervention in this subgroup of patients may cease the development of hearing loss. Thus, we propose that HFA should be performed as a routine screening not only for the study of RA but also for all of the inner ear disorders [26, 28, 43]. This should be taken into consideration not only before a treatment which may cause possible inner ear damage is performed but also along a long-term treatment such as the one received in patients with RA. We recommend a yearly HFA to be performed in patients with RA and other autoimmune diseases.

Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Anexo 2:

“Intratympanic Methylprednisolone for sudden sensorineural hearing loss: subjective and objective outcomes”.

En este trabajo el objetivo fue evaluar la efectividad y seguridad de la aplicación intratimpánica de corticoides en pacientes con hipoacusia neurosensorial súbita comparando de manera subjetiva y objetiva los resultados y realizando además una revisión bibliográfica sobre la administración transtimpánica de la metilprednisolona. Se concluyó que la inyección intratimpánica de metilprednisolona es una opción válida y segura como tratamiento de rescate, así como de primera línea. Fue la primera vez que se estableció una correlación entre los resultados subjetivos y objetivos.

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Intratympanic Methylprednisolone for Sudden Sensorineural Hearing Loss: Comprehensive Re Examination of the Model

Abstract

Objective: To evaluate the effectiveness and safety of Intratympanic methylprednisolone injection in patients with sudden sensorineural hearing loss (SSNHL) by means of a comparison between subjective and objective outcomes and a review of the literature regarding methylprednisolone transtympanic administration.

Data Sources: An electronic database search (MEDLINE and PubMed) was performed with the objective of identifying all studies published in the English language between January 1980 and October 2014 on the treatment of intratympanic methylprednisolone injection in ISSNHL. Prospective, non-randomized, case review of patients diagnosed with ISSNHL treated with intratympanic methylprednisolone from January 1, 2012 to June 1, 2014.

Study Selection: Twenty-seven articles describing intratympanic methylprednisolone injection in ISSNHL

Data Extraction: Mean, standard deviation and extreme values were presented in continuous variables; absolute value and proportions for categorical variables. The results were expressed as mean ± standard deviation (SD). The comparison between categorical variables was evaluated by the χ^2 test or the continuity correction χ^2.

Data Synthesis: The entire analysis was performed using the SPSS package, version 15.0 (SPSS package Inc.)

Conclusion: Intratympanic methylprednisolone injection is a valid and safety option as a rescue therapy and also as first line treatment according to objective and subjective outcomes. It is the first time in which a correlation between subjective and objective outcomes could be established.

Keywords: Inner ear; Methylprednisolone; Intratympanic therapy; Sudden sensorineural hearing loss; steroids

Research Article

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Abbreviations: SSNHL: Sudden Sensori Neural Hearing Loss; ISSHL: Idiopathic Sudden Sensori Neural Hearing Loss; ITS: Intratympanic Steroids.

Introduction

Since idiopathic sudden sensorineural hearing loss (ISSHL) is a true otologic emergency, a clear definition is mandatory. Although most authors agree that ISSHL can develop in 72 hours, there is controversy in considering the defining intensity of the hearing loss [1-4]. The natural history of ISSHL has not been elucidated; spontaneous recovery has been reported to occur in approximately 30-60% of cases [5] and some cases recover so quickly that they do not seek medical attention.

The diagnosis of ISSHL is currently debatable due to the fact that the natural history of ISSHL is unknown and there is no single therapy that has been demonstrated to be effective. Due to ISSHL is a diagnosis of exclusion, the more extended and thorough the diagnostic investigation is conducted, the less idiopathic causes are found. Since the diagnostic work-up must exclude any identifiable causes, patients should be followed for at least 12 months, time enough to consider the diagnosis of ISSHL [6].

Although the exact cause of ISSNHL is still controversial, the main theories include viral infection of the labyrinth, vascular insult and autoimmunity. The lack of consensus in the management of ISSNHL is due to difficulty in finding the real cause of the hearing loss. Most recoveries occur within the first two weeks after the onset. Recovery is mainly affected by the degree and type of hearing loss and time to therapy. Attempts to look for a consensus are recommended [7]. If for refractory hearing loss the expected recovery is extremely low, for a first-line therapy a confounding factor is the presence of the spontaneous recovery. However, when a patient seeks for medical advice and attention, usually days or weeks after the onset of the hearing loss, we can hypothesize that spontaneous recovery of hearing is unlikely. Therefore, in such a situation, no treatment or the use of placebo may be questionable and raises ethical dilemmas.

Systemic steroid therapy is a common treatment modality, with a reported success rate between 5% and 89% [8-10]. One of the main advantages of systemic steroids is their ability to arrest an immune reaction in the context of an autoimmune disorder. When the inner ear is the only organ affected by immunological responses, e.g. ISSHL with suspected immunologic origin, a

clinical profile for the diagnosis is valuable and corticosteroids achieve the best outcomes in such as patients [11]. Despite their widespread use, there is little consensus on the effectiveness of oral steroids and recent systematic reviews have called standard oral steroid therapy into question [12]. For patients failing to recover after initial oral or intravenous steroids, there were no additional options.

Silverstein et al. [13] first applied the Intratympanic steroid injection as treatment of ISSHL. Most of the studies regarding Intratympanic steroids (ITS) have shown their efficacy as an initial treatment for ISSNHL (as the first treatment without systemic corticosteroids), adjuvant therapy (concomitantly with systemic corticosteroids) or as a salvage therapy for the refractory ISSHL patients (started after systemic corticoid therapy has failed). The aims of the present study were the determination of the effectiveness and safety of Intratympanic methylprednisolone to treat ISSHL by means of a comparison between subjective and objective outcomes and a review of the literature regarding to trans tympanic intervention focused on methylprednisolone administration.

Patients and Methods

Prospective, non-randomized, case review of patients diagnosed with ISSNHL treated with Intratympanicl methylprednisolone.

Inclusion criteria

a) SSNHL, which was defined as a sudden unilateral sensorineural hearing loss of at least 30 dB at 3 contiguous frequencies over a period of ≤ 3 days.

b) Time from the onset of hearing loss to the treatment was ≤ 14 days.

c) No history of ear diseases.

d) No specific causes for the SSNHL after proper investigation.

e) Recovered less than 50% of their pre-loss hearing during systemic steroid treatment and presented for Intratympanic therapy within 1 month (up to 34 days) of onset (rescue group) or subjects affected by systemic disorders that do not recommend systemic steroid therapy (first line group).

The exclusion criteria were defined as follows

a) Bilateral hearing loss

b) Other contraindications to the administration of Intratympanic (IT) steroids

c) The presence of a neoplasm or recent chemotherapy or radiation therapy

d) Congenital cochlear malformations or the presence of otitis media with an abnormal Tympanogram

e) Recent use of ototoxic medications

f) Liver or renal dysfunction, and/or pregnancy. Our local ethical committee granted approval for the study, provided that the patient made the choice of treatment. All the patients included in the study were informed about each treatment and selected their preferred type of therapy of their own free will.

Rescue group

Seventeen patients had failure of systemic therapy and received injections as a rescue line. Of them, three were treated with intravenous methylprednisolone 125-500 mg for 72 hours, fourteen received oral steroids (methylprednisolone or deflazacor) 1mg/kg/day tapered in three weeks and two were treated in other hospital and we could not get the records.

First line group

Four patients were treated with local steroids because of their medical records: one had a vascular necrosis of hip, one had schizophrenia and two had hypertension treated with several drugs. Subjects received 4 methylprednisolone injections through the tympanic membrane within a 1-week period. Most injections were administered in the outpatient department of otolaryngology by one of the authors (JR G-B).

Intervention

The patient was placed in a supine position with the affected ear angled toward the ceiling. The external ear canal was cleaned of debris and the tympanic membrane was visualized with an operating microscope. Local anaesthetic of topical 5% lidocaine warmed to body temperature solution filled the external canal and tympanic membrane. A 1-ml tuberculin syringe and a 27-gauge spinal needle slightly angled to allow a proper visualization of the puncture site were used to inject 0.3-0.5 ml of 40 mg/ml methylprednisolone solution which penetrated the tympanic membrane at the posterior–inferior quadrant, avoiding puncturing in the same place twice during the course of the treatment. The injection was administered slowly so that the solution pooled around the round window niche, completely filling the middle ear cavity leaving any surplus fluid in the external auditory canal. The patient was instructed to avoid swallowing; speaking or moving in the supine position with the head tilted 45 degrees to the healthy side for 30 minutes to provide a maximal absorption of the medication through the round window and to prevent drug leakage through the eustaquian tube. The dose varied due to subject specific factors, although in most cases, at least 0.3 ml was injected.

Hearing evaluation

Patients were evaluated with pure-tone audiometry before each injection and 1 month after steroid injection. The mean value for the pre treatment and post treatment was calculated as the mean value at each of the 8 frequencies (125, 250, 500, 1000, 2000, 4000 and 8000 Hz) and also at 5 frequencies (250, 500, 1000, 2000, 4000).

Standard Assessment

The standard assessment included routine audiometric testing (PTA at five frequencies and impedance audiometry), serological tests (ANA, FTA, inmunophenotype of blood T cells), serum glucose measurement, coagulation and MRI of posterior fossa.

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Outcome assessment

Hearing response was defined as an improved pure-tone average ≥10 dB, Subjective outcome was considered when a statistical difference in a visual analogue scale (VAS) pre treatment and post treatment was observed. The visual analogue scale was used to describe hearing loss and tinnitus in a subjective way. It was expressed from 0 to 10, indicating that 0 was no symptom and 10 the most annoying o incapacitating symptom.

Statistical analysis

Mean standard deviation and extreme values were presented in continuous variables; absolute value and proportions for categorical variables. The results were expressed as mean standard deviation (SD). The comparison between categorical variables was evaluated by the χ^2 test or the continuity correction χ^2.The results for each frequency between pre and post comparisons were analysed using *t*-tests for paired data. The mean of the differences have been estimated by calculating their confidence intervals of 95%. The Pearson correlation coefficient for the measures of relationship VAS and the global mean. The box plot was drawn to illustrate the median, quartiles and extreme values of VAS. The level of statistical significance was $p<0.05$ and two side. The entire analysis was performed using the SPSS package, version 15.0 (SPSS package Inc.)

Results

Twenty-one patients enrolled in the study. There were 12 males and 9 females. The mean age was 46 years and ranged from 27 to 85 years. Seventeen patients (80.95%) had failure of systemic therapy and received injections as a rescue line. Of them, three were treated with intravenous methylprednisolone for 72 hours, fourteen received oral steroids (methylprednisolone or deflazacor) for 21 days and two were treated in other hospital and we couldn´t get the records. The mean days from the onset of systemic therapy to the injections were 11.5 days. Four patients (19.04%) had contraindications for systemic therapy: two with hypertension, one had a previous a vascular necrosis of the hip and one had schizophrenia. In these cases, the tympanic injection was their first-line treatment

All patients received one weekly injection for 4 weeks. Eleven patients (52.3%) did not express any complication. Seven patients (33.3%) experienced pain that disappear in minutes, four patients (19%) described dizziness and one (4.8%) had burning sensation. There was a case of perforation in a patient that had a monomer tympanic membrane. The mean value for hearing loss in the VAS before and after the treatment was 8.6 and 1.4, respectively. The mean of the difference in score was 7.1 (5.1- 9.2; $p< 0.001$) (Figure 1).

The mean value for tinnitus in the VAS before and after the treatment was 7.8 and 2.9, respectively. The mean of the difference in score was 4.9 (3.1- 6.6; $p< 0.001$).Of the 21 patients, 14 (66.7%) presented a PTA average > 10 dB hearing thresholds at 250-500-1000-2000-4000 Hz before and after the treatment were 59.0 dB and 40.4 dB, respectively and the improvement was 18.75dB ($p<0.001$). Table 1 represents each frequency (125-8000 Hz) with their means and standard deviation. We also used these frequencies to get the mean of hearing loss with the VAS and it was 7.4 before and 3.0 after, with a mean of 4.4 ($p<0.001$). The Pearson correlation between VAS (hearing loss) and the PTA average pre treatment was 0.53 ($p = 0.13$) and post treatment was 0.67 ($p= 0.01$).We separate the total of patients in the two subgroups (first line and rescue) to evaluate if there is a significant difference in the results. In the first line group (4 patients) we got that the PTA pre treatment and post treatment using the five frequencies (250-4000 Hz) were 46.8 dB and 29.3 dB and the improvement was 17.5 ($p= 0.138$). On the other hand, in the rescue group (17 patients), the PTA pre treatment and post treatment were 61.9 dB and 43.1 dB and the improvement was 18.8 ($p< 0.01$).

Table 1: Hearing thresholds before and after injections in each frequency.

Frequency	Mean Pretreatment(dB)	SD pre Treatment(dB)	Mean post Treatment(dB)	SD post Treatment(dB)	Improvement(dB)	CI 95%	p
125	52.38	22.83	35.48	24.13	16.91	7.2-26.6	0.002
250	50.95	26.58	35.48	27.69	15.48	1.3-29.7	0.034
500	59.05	25.27	38.81	28.80	20.24	9.9-30.5	0.001
1000	59.05	23.27	40.95	25.72	18.10	9.7-26.5	< 0.001
2000	56.67	19.06	40.24	24.87	16.43	6.9-25.8	0.002
4000	65.00	22.97	46.67	24.51	18.33	9.8-26.8	< 0.001
8000	68.25	25.66	49.75	28.77	18.50	9.5-27.4	< 0.001

Discussion

ISSHL can be considered the result of abnormal activation of cellular stress pathway involving nuclear factor κβ in supporting cells and spiral ligament fibrocystic resulting in the production of inflammatory cytokines and other stress-related proteins that can disrupt the homeostatic balance of the inner ear [6,14]. Traditionally the effect of corticoids has been attributed to the anti-inflammatory and immunosuppressive activity including down-regulation of local proinflammatory cytokines (IL-1, IL-6, TNF-α) [15], neuroprotective, antioxidant and ant apoptotic effects, ion homeostasis (up regulation of aquaporins, increasing Na+ -K+ exchange in the stair vascular is and direct effect on connexion-protein expression) and promotion of cochlear blood flow. Furthermore, glucocorticoids and mineral corticoid

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receptors have been demonstrated in the human inner ear with the highest concentration in the spiral ligament [16].

Several trials showed that Intratympanic treatment was not inferior to oral steroid in hearing recovery [17-22]. Although Intratympanic steroids for salvage have not yet been established as the gold standard for patients with incomplete recovery from ISSHL, mounting evidence for their effectiveness has been reported [23-25]. Although dramatic recoveries in patients with profound ISSHL after salvage treatment with Intratympanic steroids are rare. The injections were offered to patients because we consider unethical not giving an alternative in patients with risk factors to systemic therapy. The Trans tympanic route has 2 advantages; firstly, it allows a greater concentration of drugs in the perilymph and secondly, it minimizes systemic effects and absorption. Side effects of systemic steroids can greatly compromise a person's quality of life and hinder their capacity to work throughout the treatment period [26].

Based on Parnes et al report [27] in which methylprednisolone presented the best absorption profile in both perilymph and endolymph after trans tympanic administration, we only use methylprednisolone for Intratympanic therapy and focused on this drug the present review. Trans tympanic corticosteroid treatment, however, has potential limitations, such as the presence of barriers and air bubbles in the round window niche [28] and loss of drug down the Eustachian tube. Intratympanic steroid injection is an effective, safe, cheap and well-tolerated office based-procedure for the treatment of ISSHL.

Injection procedures include Intratympanic injection using a needle puncture technique, Intratympanic injection after myringotomy, steroid administration through tympanostomy tubes and continuous delivery of steroids via a micro pump embedded in the round window niche (Table 2). Most authors achieve local anaesthesia of the external auditory canal and tympanic membrane by different methods (Table 3) in order to make comfortable the procedure. In our experience the most safety and simple method of achieving local anaesthesia is by means of topical lidocaine 5% solution warmed to body temperature. Infiltration of the vascular strip could cause blister formation in the external auditory canal skin and diffusion of the anaesthetic to the middle ear cleft resulting in vertigo and transient facial palsy. Injection of a drug mixture consisting of methylprednisolone and lidocaine [29] may interfere with the effect of the steroid, increases the potential risk of sudden vertigo due to lidocaine diffusion to the labyrinth, may be as painful as an IT injection without any previous local anaesthesia [30] and adds another variable for the outcome evaluation. The reason for the pain reported in patients undergoing trans tympanic injection could be the pH of the steroid solution [31] because of the volume needed, whereas with targeted delivery administration by using a round window membrane micro catheter [32], the lower volume is less likely to cause discomfort. Potential disadvantages of micro catheter include the risk and expense of general anaesthesia, operating room time, perforations of the tympanic membrane and price of the device.

Table 2: Comparison of administration delivery of local methylprednisolone.

Administration	Author
Injection	William H Slaterry [8] Dallan I [54] John Xenellis [24] Fitzgerald [44] Rahmi Kiliç [39] Guillermo Plaza [47] Dallan I [46] Yang Chen [29] Igor Texeira [48] Necmi Arslan [38] Dallan I [42] Peng Li [35] Steven D Rauch [17] Yide Zhou [25] Tomás Labatut [34] Onur Gundogan [41] Our study
Micropump	Richard D Kopke [32] Stefan Plontke [37] France Van Wijck [45] Wandong She [49] Sébastian Barriat [43]
Tube	Gerard J Gianoli [2] Avik Banerjee [22] Jürgen Lautermann [36]

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Table 3: Comparison of anesthesia in methylprednisolone local administration.

Anesthesia	Author
Alphacaine [articaine hydrochloride 40mg epinephrine 0006 mg/ml]	Sébastian Barriat [43]
EMLA	Gerard J Gianoli [2] Igor Texeira [48]
General	Richard D Kopke [32]
Lidocaine	William H Slattery [8]
Lidocaine 1% + adrenaline 1:100000 injection	France Van Wijck [45] Tomás Labatut [34]
Lidocaine 10% [cotton ball soaked]	Onur Gundogan [41]
Lidocaine hydrochloride 2% added in the solution	John Xenellis [24] Rahmi Kiliç [39]
None	Necmi Arslan [38] Rahmi Kiliç [39]
Not specified	I Dallan [54] I Dallan [46] Stefan Plontke [37]
Phenol	Gerard J Gianoli [2] Avik Banerjee [22] Fitzgerald [44] Guillermo Plaza [47] Peng Li [35] Steven D Rauch [17] Benjamin J Wycherly [50] Yide Zhou [25]
Tetracaine	Yang Chen [29] Wandong She [49]
Topic lidocaine	Our study

Concerns with steroid administration through a tympanostomy tube are related to the dose administered, in many cases, by the own patient, and the higher risk of perforation of the tympanic membrane [22,33]. Needles of different diameters have been used for ITS injection. In our study we used a 27-gauge spinal needle, what facilitates the collapse of the injection site when the needle is pulled out and keeping the fluid in the middle ear [34]. The patient is placed supine with the treated ear upward for 20-30 minutes in most studies. The amount injected in the middle ear in published papers ranges from 0.3 to 0.5 mL, which is approximately the middle ear volume. In our study we used an approximate dose of 0.5 mL of 40 mg/mL. The optimal dose, however, is debatable and it is very difficult to estimate taking into consideration that the amount of drug filling the middle ear cleft could be reduced by the mixture with local anaesthesia or sodium bicarbonate, the middle ear cleft size, the existence of adhesions in the round window niche and the loss through the eustaquian tube [35]. Another concern are the exact treatment duration and schedule. Most protocols include from 1 to 4 injections with different time courses of administration (Table 4).

In the present study we performed 4 injections with one-week interval. Perhaps due to the pharmacodynamics of corticosteroids in the inner ear, the IT injections might be done with at least 24-hour intervals, but the risks of overdose and perforation of the tympanic membrane advise a more prolonged interval. The reported effective rates ranges from 12 to 100% and the average

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PTA improvement ranged from 8 to 62 dB [36,37]. Most authors include 0.5, 1, 2, and 4 kHz. The most widely adopted criteria for hearing recovery is the improvement of 10 dB in PTA after treatment [38,39]. Since this criterion can overestimate the effectiveness of steroids, we included all frequencies (0.125 to 8000 Hz) for calculating hearing recovery. According to this criterion, 66.7% of our patients showed a positive response. However, we could not establish significantly differences between the rescue group and first line group of patients due to the low number of cases in the first line group. Efficacy of treatment was also categorized according to Siegel's criteria [40,41] relative gain [42] and the speech reception thresholds (SRT), speech discrimination testing (SDS) and the maximum speech intelligibility [43-45].

Table 4: Comparison between intervals of methylprednisolone administration.

Interval	Author
1 alternating days injection [total 3]	Igor Texeira [48]
1 alternating days injection [total 4]	Yide Zhou [25]
1 alternating days injection [total 5]	Necmi Arslan [38]
1 consecutive diary injection [total 5]	Jürgen Lautermann [36]
1 injection	I Dallan [54] I Dallan [46]
1 injection each 2 days [total 4]	Yang Chen [29]
1 injection each 3 days [total 4]	Peng Li [35] Onur Gundogan [41]
1 injection each 3 days [total 5]	Rahmi Kiliç [39]
1 injection or more	I Dallan [42]
1 weekly injection [total 3]	Fitzgerald [44] Guillermo Plaza [47] Benjamin J Wycherly [50]
1 weekly injection [total 4]	Our study
2 weekly injections until improvement	Avik Banerjee [22]
Not specified	France Van Wijck [45] Sébastian Barriat [43]
Perfusion 4 weeks	Stefan Plontke [37]
Perfusion for 10 days	Wandong She [49]
Perfusion for 14 days	Richard D Kopke [32]
Separated injection in 10-14 days [total 4]	Gerard J Gianoli [2] William H Slattery [8]

Many authors agree that patients that started therapy soon after failures of systemic therapy was detected had an evident advantage [46,47]. In the present study time elapsed from onset of the symptoms to the beginning of the ITS injections was 11.3 days. This short period could represent a prognosis factor in the outcome of ISSHL and it was similar to observed by other authors [8,32,48,49]. A significantly increased response rate was found in patients having an audiogram >5 weeks after the first dose of ITS [50]. In our protocol we performed the last audiogram for the outcome assessment 4 weeks after the last ITS administration.

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This follow-up would identify early versus late responders in base to different mechanisms of damaging the inner ear.

Although the possible ototoxic effect of IT steroids has been ruled out in experimental and clinical studies [51-53] one patient with worsening of the PTA with repeated injections of methylprednisolone has been reported [54]. This worsening may represent a dose-effect response: a higher than therapeutic dose might have damaged the inner ear . In our study, no patient experienced worsening of their hearing. Although IT steroid procedure was well tolerated, in our study seven patients (33.3%) experienced pain that spontaneously disappearing in minutes or easily controlled by the administration of paracetamol. A recent report that compared the pain level of local anaesthesia, showed no difference in pain intensity among three methods (application of EMLA cream, subcutaneous injection of lidocaine 1% with 1:100.000 epinephrine and IT injection without previous anaesthesia). A burning sensation around the ear was one of the most frequently encountered side effects of IT methylprednisolone, and it resolved over a period of 10-20 minutes after the injection in most patients [55]. In Rauch et al study (17), 54 % of patients experienced pain.

Effective drug delivery into the inner ear can stimulate the vestibule and induce dizziness, possibly due to caloric effect, which implies a good prognosis [29]. Four patients (19%) complained of vertigo (despite of the solution was warmed to body temperature) or an increase in tinnitus during the injections, but these complaints resolved within minutes. Tympanic membrane perforations are usually observed if myringotomy had been done, and usually recover easily [32]. In our study only one patient developed a tympanic membrane perforation. The use of a needle of 27-gauge that causes a small hole and the fact that injections were repeated at one-week intervals could facilitate the healing of the tympanic membrane thus justifying the low percentage of perforations found in our patients.

We propose the addition of a VAS (Visual Analogue Scale) to contribute to the evolution assessment of hearing recovery and tinnitus amelioration in ISSHL, based in a preliminary report presented in 2013 [56]. A statistically difference in the VAS before and after the treatment in tinnitus and hearing loss could be observed ($p< 0.001$). Correlation between VAS (hearing loss) and the PTA average pre-treatment and post treatment was statistically significant as well ($p = 0.01$). This is the first time, in our knowledge, that such a correlation has been reported

Conclusion

ISSHL remains a challenging clinical problem. ISSHL can be considered the result of abnormal activation of cellular stress pathway inside the inner ear resulting in the production of inflammatory cytokines and other stress-related proteins that can disrupt the homeostatic balance of the inner ear. The main mechanism of action of steroids on cochlear function has been attributed to the anti-inflammatory and immunosuppressive activity. Tran's tympanic route allows a greater concentration of drugs in the perilymph minimizing systemic adverse effects. Since methylprednisolone presented the best absorption profile we used this drug for treating patients affected by ISSHL.

Intratympanic steroid injection is an effective, safe, cheap and well-tolerated office based-procedure for the treatment of ISSHL. The low rate of complications and the hearing outcomes support its use not only as a rescue therapy but also as first line treatment. Subjective outcomes regarding to hearing loss and tinnitus strongly advocate the use of Intratympanic injection of methylprednisolone in ISSHL. It has to be considered that the second group has a small number of patients to extract definitive conclusions despite the results and that a study with a big number is needed to confirm the results.

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Anexo 3:

“Extended high frequency audiometry can diagnose sub-clinic involvement in a seemingly normal hearing systemic lupus erythematosus population.”

La hipoacusia neurosensorial debe tenerse en cuenta entre las presentaciones clínicas conocidas del Lupus Eritematoso Sistémico. Los resultados de este estudio confirman la utilidad de la audiometría de altas frecuencias como necesaria en la evaluación y detección temprana de la hipoacusia en dichos pacientes facilitando así una posible modificación del tratamiento que esté recibiendo o añadir algún tratamiento preventivo para la hipoacusia.

Se correlacionó la hipoacusia neurosensorial con la severidad de la enfermedad y los parámetros inmunológicos asociados.

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ORIGINAL ARTICLE

Extended high frequency audiometry can diagnose sub-clinic involvement in a seemingly normal hearing systemic lupus erythematosus population

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ABSTRACT

Conclusions: Sensorineural hearing loss must be considered within the clinical picture of systemic lupus erythematosus. The results confirm the usefulness of extended high-frequency audiometry in the audiologic testing of these patients, enabling the possibility of modifying or applying a preventive treatment for a possible hearing loss.

Objectives: Hearing involvement is usually under-diagnosed with routine auditory examination. This study proposes the use of extended high-frequency audiometry to achieve a correct detection of a possible asymptomatic hypoacusis in early stages of the disease. The aim of this study is to analyze the hearing levels in extended high-frequencies in these patients and to correlate the hearing loss with the severity of the disease and the immunological parameters.

Methods: A descriptive cross-sectional study was performed. Fifty-five patients with systemic lupus erythematosus were included in the study. The control group consisted of 71 patients paired by age and sex with the study population. Both a pure tone audiometry and an extended high-frequency audiometry (8–18 KHz) were performed.

Results: In total, 70% were diagnosed with sensorineural hearing loss with extended high-frequency audiometry, overcoming the results obtained with pure tone audiometry (30.9%). Statistically significant correlations were found within the patients regarding sensorineural hearing loss related with age, disease activity and cryoglobulinemia.

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Systemic lupus erythematosus; extended high-frequency audiometry; immune-mediated disease; sensorineural hearing loss

Introduction

The first time autoimmune hearing loss was mentioned was in 1979 by McCabe who described the first series of patients with progressive bilateral sensorineural hearing loss and some altered immunological testing that responded to an immunosuppressive treatment. In 2007 he published new insights regarding autoimmune disease based on his first findings in 1979 [1]. The disease affects more than 5 million people around the world, 90% of them being women. The prevalence is of ~130/100000. In the US, the African-American, Hispanic, and Asian population are usually the most affected.

Systemic lupus erythematosus (SLE) is an autoimmune chronic and multi-systemic disease, being the prototype of disease regarding immune complexes. This immune-mediated disease may be accompanied by hearing loss [2–8], the sensorineural type estimated as present in 8–28.6% [9,10] by means of Pure Tone Audiometry (PTA). A significant number of clinically asymptomatic patients with SLE have sub-dinical sensorineural hearing abnormalities (57.5%), probably of an autoimmune pathogenesis [3]. Similar results (66%) have been reported with high frequencies involving statistically significant differences when compared with the control group [4]. Nevertheless, the percentage of hearing loss reported by other authors was certainly less (8–22.5%) [5,9,10]. Clinical manifestations, laboratory findings, and disease activity parameters showed no correlation with the hearing loss. However, this might have been the result of a type 2 error (small number of patients in the sample studied) [10].

The pathogenesis of sensorineural hearing loss in SLE remains unknown, although it is related to a possible vasculitis [6,7], immune-complex deposits in the stria vascularis or in the endolymphatic sac, and a direct cytotoxic or thrombotic action [8].

The aim of this work is to assess the real prevalence of sensorineural hearing loss in patients with SLE by means of an advanced audiometric analysis, based on extended high-frequency audiometry (HFA), evaluating its efficiency and clinical usefulness to incorporate it into the routine (normal) audiologic examination. To our knowledge few studies have been performed before, using extended high frequency audiometry to determine a possible early hearing loss in patients with SLE which may allow a preventive or therapeutic approach if necessary [11]. Likewise, we also investigate if any immunological parameter is found to be related with hearing loss.

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Materials and methods

Cross-sectional descriptive study, comparative and control groups were matched for age and sex.

Inclusion criteria

Both a complete medical history and an ENT examination were performed, using the following *inclusion criteria*: patients diagnosed with SLE, both sexes, and aged between 20–60.

The patients met the 1997 Update of the 1982 American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus [12]. All of the patients included in the study were of Spanish origin.

Control group

Seventy-one patients (142 ears) were consecutively recruited in the 'Area 9' of Madrid, from January 2010 to February 2011. The control group was composed of patients with a normal state of health; free from all signs or symptoms of ear disease and from obstructing wax in the ear canal; no history of exposure to noise, potentially ototoxic drugs or genetic/hereditary hearing loss that attended our ENT department for head and neck or rhinologic disorders.

Experimental group

Fifty-five patients with SLE (110 ears), both sexes between 20–60 years old, were diagnosed and chosen.

In association with the Rheumatology and Nephrology departments from the 'Severo Ochoa' University Hospital, clinical data was obtained based on a protocol, of all the patients that were attended from January 2010 and February 2011. At the end of each week the data was gathered and all their medical records were revised. Next, we registered every feature regarding each patient, their disease, and treatment received.

Every variable was measured and analyzed only once and by the same investigator to maintain its accuracy.

Exclusion criteria

Control group

- Age: more than 60 years.
- Family history of hearing loss.

Patients who suffered from another immune-mediated disease, traumatic brain injury, middle ear diseases or surgery, previous treatment with chemotherapy or radiotherapy, treatment with diuretics, Menière's disease, cardiovascular diseases, metabolic diseases, HIV or syphilis, exposure to noise, and the use of known ototoxic medication before the study began.

Experimental group

The experimental population could not suffer from another immune-mediated disease different from SLE, and was required to meet the other inclusion and exclusion criteria of the study population.

Extended high-frequency audiometry of 8000–18 000 Hz was performed in the whole experimental group [13].

Demographic (age, sex), auditory (auditory thresholds with PTA and HFA), related to the rheumatological disease (activity, duration, years of exposure to the ototoxic treatment and immunological analysis) and related to the ENT clinical cochleo-vestibular variables were part of the study.

Hearing examination

Audiometry

The initial otologic examination included an otoscopy and an audiologic evaluation with a PTA and a HFA. Based on a questionnaire (Annex A in ISO 389-9: 2009) all the subjects suitable for inclusion were evaluated according to a written protocol based on ISO 389-9 recommendations on the determination of reference hearing threshold levels. Hearing loss has been considered as an average loss of more than 30 dB (500 + 1000 + 2000 + 4000 Hz). The expected conventional frequency pure-tone hearing thresholds of otologically normal subjects are published in ISO 7029 (International Organization for Standardization, 2000). The current ISO standard does not include subjects above 70 years old. Standard references in the EHF range (8–16 kHz) are available in the ISO 389-5 (2006), although these are limited to a small number of specific earphones [13].

For each test frequency, the signal was manually increased by steps of 5 dB until the test person responded, after which the signal was decreased by 10 dB and increased by 5 dB until a response was received. The intensity to which the listener responded three out of five times was recorded as the actual threshold. The audiometric procedure was conducted using continuous stimuli of 1–2 s (IEC 60645-1: 2001). Masking was used.

The pure-tone hearing thresholds (125–8000 Hz) were measured with a manual audiometer (Madsen Orbiter 922, version 2; Madsen Electronics, Taastrup, Denmark) and equipped with TDH-39 supra-aural earphones (Telephonics Co., Farmingdale, NY).

HFAs thresholds (9, 10, 11.2, 12.5, 14, 16, and 18 kHz) were determined using a Madsen clinical audiometer (Madsen Orbiter 922, version 2; Madsen Electronics, Taastrup, Denmark) with a Sennheiser HDA 200 closed circumaural earphone (Sennheiser Co, Wennebostel, Germany). All testing equipment for audiometry was calibrated according to ISO 389-5 (International Organization for Standardization, 2006) and the manufacturer's recommendations. Threshold measurements were conducted in a soundproof chamber. The threshold was defined as the lowest decibel hearing level at which responses occurred in at least 50% of a series of ascending trials (ANSI, 2004).

Formal audiometer calibration was carried out in accordance with the relevant ISO 389-1 (1998) and IEC 60645-1 (2001) standards. Transducers were calibrated according to ISO 389-1 (1998) and IEC 60318-1 (2009). The calibration instrumentation included an IEC 318 artificial ear (Brüel &

Kjael type 4153), a half-inch pressure microphone (Brüel & Kjael type 4134) with a slotted grid fitted, an IEC type 1 sound level meter (Brüel & Kjael type 2235), and a filter set (Brüel & Kjael type 1625) [13,14].

Laboratory analysis

The whole study population underwent an immunological analysis of all those parameters that show immunological activity in SLE such as C-Reactive Protein; CRP, Erythrocyte Sedimentation Rate; ESR, Rheumatoid Factor (RF), Antinuclear Antibodies; ANAS, Acute Phase Reactants (APR, Anti-Ro/SS-A, Anti-La/SS-B), serum cryoglobulins, anti-cardiolipins (aCL), and anti-thyroid antibodies.

SLE activity

The disease activity (SLE) was evaluated in the Rheumatology department according to the Disease Activity Index 2000 (SLEDAI-2K), which was performed in the first consult and in all the follow-up consults of each patient.

Disease activity is considered positive when the SLEDAI-2K rises above 3.

Ethics

All the procedures used in this study and practiced on each patient were in agreement and regulated with approval from the 'Severo Ochoa' Hospital (Madrid) ethical code identified by the *MINUTE: 11/09, 25/11/2009, IEC (Independent Ethics Committee) Internal code: 431-A (65/09)* and following the international Declaration of Helsinki (1983). Informed consent was obtained from all subjects, after being informed with detail about the purpose of the study, according to the recommendations from the Ethics Committee in our center.

Statistical analysis

The statistical analyses were achieved using the SPSS 15 (Statistical Package for the social Sciences) for Windows. Quantitative statistical methods of data analysis and qualitative methods were used. For the bivariate analysis the Chi-square test and the Fisher's exact test were used for the qualitative variables and for the quantitative variables the Student's *t*-test and the Mann-Whitney U-test. To control the possible confounding variables and possible interactions a logistic regression adjustment analysis was performed, taking into consideration the possible associations related to the patient, auditory findings, rheumatic disease, and sensorineural hearing loss being the dependent variable.

The estimate was established with 95% confidence intervals of the hearing loss prevalence in the PTA (threshold > 30 dB HL), in the HFA (according to the auditory threshold of the control population for every frequency), according to ages (ranges of 20–29, 30–39, 40–49, and 50–60 years) and both sexes, taking into consideration a p-value of < 0.05 being considered significant.

Order of the applied procedures

Variables related with hearing

The auditory thresholds from both eras were analyzed on each patient regarding low, middle, and high frequencies (up to 20 KHz) using a PTA and a HFA.

Variables regarding the rheumatological disease

- Disease activity: presence of rheumatological signs and symptoms.
- Duration of the disease: we registered date of birth, date of diagnosis of the disease, and date in which the tests were performed.
- Years of exposure to a possible ototoxic treatment: type of drug, administration via, and duration of the treatment with Antimalarials, Salicylates, and Metotrexate.
- Laboratory results and analysis: C-Reactive Protein; CRP, Erythrocyte Sedimentation Rate; ESR, Rheumatoid Factor (RF), Anti-nuclear Antibodies; ANAS, Acute Phase Reactants (APR), Anti-Ro/SS-A, Anti-La/SS-B, serum cryoglobulins, anti-cardiolipins (aCL), and anti-thyroid antibodies.

Variables related with ENT clinical features

Subjective hearing loss, vertigo and/or dizziness, and tinnitus in the experimental group.

Informed consent

Once the inclusion and exclusion criteria were applied the patients were called for an appointment to inform them of the investigation and procedures and sign the informed consent.

Results

The medium age of the patients with SLE was 41.5 years (interquartile range =31–46 years), with eight men and 47 women, giving a male/female ratio of 14.5%/85.5%. A control population of 71 subjects was studied (142 ears) belonging to the area 9 of Madrid, taken in a consecutive form, with a medium age of 38 years (20–60 years) and a female predominance (62.7%).

Regarding the control group, the hearing thresholds decreased from 125 to 2000 Hz. From 2000 Hz onwards the thresholds increased coinciding with increasing frequency and age. All the data regarding the variables and results of the study are presented in Table 1.

Pure tone audiometry

The hearing loss of the SLE population registered with PTA was 30.9% (34 ears). The type of hearing loss obtained was sensorineural. We obtained a significant difference in the auditory assessment with higher thresholds in SLE patients (arithmetic range of the frequencies 1500 Hz ($p = .036$), 2000 Hz ($p = .004$), 3000 Hz ($p = .018$), and 8000 Hz

Table 1. Table highlighting the main sociodemographic and clinical features of the patients studied.

HFA SLE	HFA, Hearing loss ($n = 77$) (70%)	HFA, No hearing loss ($n = 33$) (30%)	OR (IC95%), No adjustment	OR (IC95%), Adjustment
Gender				
Male	10 (62.5%)	6 (37.5%)	0.67 (0.22–2.03)	
Female	67 (71.3%)	27 (28.7%)	Reference	
Medium age	46 (35.5–56)	40 (32–52)	1.02 (0.9–1.05)	1.02 (0.98–1.08)
Duration of disease (years), Medium	8 (6–13)	8 (5–13)	1 (0.91–1.08)	
Rheumatologic activity	42 (80.8%)	10 (19.2%)	2.7 (1.15–6.57)*	2.6 (1.05–6.42)*
Clinical hearing loss	10 (100%)	0 (0%)	1.49 (1.3–1.71)*	1.49 (1.3–1.71)*
Vertigo/Dizziness	26 (72.2%)	10 (27.8%)	1.17 (0.48–2.82)	
Tinnitus	11 (68.8%)	5 (31.3%)	0.93 (0.29–2.93)	
Years since the beginning of treatment				
Antimalarials	6 (3.25–7)	5.5 (3.81–8)	0.99 (0.88–1.12)	
Salicylates	4 (3–4.75)	4 (2.3–4.5)	1.04 (0.61–1.76)	
Metotrexate	3 (1.5–3.58)	2 (0.08–2)	2.87 (0.82–10)	
Laboratory parameters, *n* (%)				
ESR	55 (72.4%)	21 (27.6%)	1.4 (0.6–3.39)	
CRP	60 (66.7%)	30 (33.3%)	0.35 (0.09–1.29)	0.32 (0.08–1.23)
Serum Cryoglobulins	17 (94.4%)	1 (5.6%)	9.06 (1.15–71.27)*	9.3 (1.16–74.5)*
ANAs	53 (73.6%)	19 (26.4%)	1.62 (0.7–3.77)	
RF	69 (71.9%)	27 (28.1%)	1.91 (0.6–6.04)	
Ad	27 (67.5%)	13 (32.5%)	0.83 (0.35–1.92)	
SS antibodies	18 (75%)	6 (25%)	1.37 (0.49–3.84)	
Anti-thyroid antibodies	11 (78.6%)	33 (21.4%)	1.66 (0.43–6.41)	

HFA: High frequency audiometry; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; RF: Rheumatoid Factor; ANAS: Antinuclear Antibodies; Anti-Ro/SS-A: Anti-La/SS-B; aCL: anti-cardiolipins.
*$p < .05$.

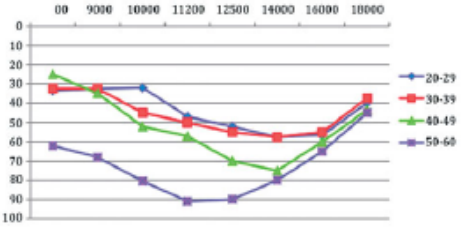

Figure 1. Auditory thresholds with high frequency audiometry according to age range of the study population with SLE. Arithmetic means (*y*-axis: intensity, dB; *x*-axis: frequency, hertz, or Hz). The total number of patients analyzed were 55 (110 ears): five from 20–29, 18 from 30–39, 10 from 40–49, and 22 from 50–60 years.

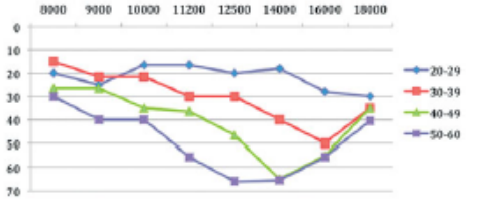

Figure 2. Auditory thresholds with high frequency audiometry according to age range of the control population. Arithmetic means (*y*-axis: intensity, dB; *x*-axis: frequency, hertz, or Hz).

($p = .031$) when comparing the patients with the control population. There were no cases of conductive or mixed hearing loss. We observed that in patients with SLE a statistically significant relationship exists between the hearing loss diagnosed by PTA and the age of the diagnosis (OR =1.03 (0.98–1.08)).

Extended high-frequency audiometry

The prevalence of high frequency sensorineural hearing loss in patients with SLE diagnosed by HFA was 70%. We compared the arithmetic mean of the auditory thresholds obtained in the cases of SLE and the controls and we did observe a significant difference in all the frequencies starting at 8000 and up to 18 000 Hz ($p < .05$), except in the frequencies of 9000 Hz and 14 000 Hz. The results show deterioration in the hearing levels of the patients with SLE in all the ranges of age, especially from 50 years on (Figures 1 and 2).

Concerning gender, we did not find any significant differences between the mean of the auditory thresholds of all the frequencies from 8–18 kHz, among both sexes.

Immunological study

In SLE patients, the activity of the disease (Odds Ratio (OR) = 2.6 (1.05–6.42)) and the serum levels of cryoglobulins (OR = 9.3 (1.16–74.5)) were associated with the high frequency hearing loss.

From the 55 patients with SLE that were analyzed, nine patients had positive serum cryoglobulins, and only one of them had no association with high frequency hearing loss.This is a reason why we consider that the positivity of serum cryoglobulins determines a possible association with sensorineural hearing loss in SLE.

Comparison of PTA and HFA

Sensorineural hearing loss diagnosis in SLE was 70% with HFA and 30.9% with PTA. The risk of diagnosing hearing loss with HFA is 33.6-times higher than with PTA (OR = 29 (4.8–1184.43)).

Medication administered

The doses of the medications received were: 100–400 mg/day of Hydroxychloroquine, 178–250 mg/day of Chloroquine,

7.5–15 mg/weekly of Methotrexate, 2.5–10 mg/day of Prednisone, and 100 mg/day of Salicylates.

Discussion

SLE can produce a sensorineural hearing loss as happens in other autoimmune diseases [9].

The etiology of the sensorineural hearing loss remains unclear. In SLE, a vasculitis is postulated as a possible cause, or thrombosis (when associated with antiphospholipid syndrome) [7–14], or the fact of immune-complexes depositing in the inner ear [15].

Since Bowman's initial report in 1986 in which SLE was not considered as a possible cause of hearing loss, along the years the number of patients with this symptom have been increasing thoroughly from 8% [6] to 66% [4]. Traditionally, PTA has been used to assess possible hearing loss in patients with SLE. In a 10-year follow-up in young SLE patients, PTA could not establish a conclusive hearing loss [15]. Even though the aim of our study is to assess hearing loss with HFA, we wanted to explore hearing loss first with PTA (the traditional method). In our study, 30.9% of patients with SLE showed sensorineural hearing loss diagnosed by PTA, as with other studies [4,16]. This sensorineural hearing loss was symmetrical and bilateral in 58.3% of these cases, similar to previous reports [4,9,16].

HFA in SLE

Since the ages of most of the study patients are out of the range of a possible presbyacusis, the results regarding hearing loss can be attributed mainly to SLE.

Sensorineural hearing loss by HFA in our patients with SLE was documented in 70% of the cases (77 ears), more than double those with the PTA. In the revised bibliography, percentages of hearing loss are not specified only distributed among high frequencies.

Comparing the results of the population of SLE with HFA with those of the control population, we find significant differences in all the frequencies, except in 9000 and 14 000 Hz, which were not significant ($p = .06$ and $p = .057$, respectively).

Our results differ from those obtained from Karabulut et al. [11], who describe significant differences in the frequencies 10 000 and 12 000 Hz (not in 9000 and 14 000 Hz as we did) when comparing the patients with SLE with those of the control population. These frequencies (14 000 and 16 000 Hz) are usually frequencies affected by noise [17]. Different environmental noise trauma could be the responsible agent.

We didn't find any statistically significant differences, between men and women, such as other authors did [11], and we also did not obtain a significant correlation with age.

We found a significant correspondence between the sensorineural hearing loss determined by HFA and the activity of the disease. In our study we didn't find any statistically significant correlations between the sensorineural hearing loss found by PTA or by HFA and the years of treatment with salicylates, methotrexate, and anti-malarial medication in agreement with other authors [4,9]. In total, 94.4% of the patients with hearing loss detected with HFA presented cryoglobulinemia. Nevertheless, only 33% of patients with hearing loss detected with PTA presented cryoglobulinemia. We obtained a significant correlation between the sensorineural hearing loss detected by HFA and the presence of cryoglobulinemia ($p = .013$), with an OR >1, which means that it is higher than 1 (positive), indicating it has a possible association with hearing loss in patients with SLE. Other studies have not established any correlations between immunological abnormalities and sensorineural hearing loss in SLE patients [18].

In conclusion:

1. There is a predisposition to develop high frequency sensorineural hearing loss in patients with SLE with a prevalence in our study of up to 70% determined by HFA.
2. The positivity of serum cryoglobulins determines a possible association with sensorineural hearing loss in SLE. More research is needed to see if it can be considered a laboratory marker of hearing loss in SLE.
3. More cases of sub-clinical hearing loss were diagnosed with HFA than with PTA.

These results suggest and recommend that audiological assessment should be done not only with PTA but also HFA in patients with SLE in order to diagnose a possible subclinical hearing loss and modify the ongoing treatment or add a therapy to prevent a possible progression of hearing loss [19,20].

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Anexo 4:

“Audiometría con extensión en altas frecuencia (9000 – 20000 Hz). Utilidad en el diagnóstico audiológico.”

La detección precoz y el tratamiento adecuado de la hipoacusia es fundamental para minimizar las consecuencias de la pérdida auditiva. Además de la audiometría convencional (125-8.000Hz), disponemos de la audiometría con extensión en altas frecuencias (9.000 - 20.000Hz), que puede ser de gran utilidad en el diagnóstico precoz de hipoacusia en ciertas patologías, como es el efecto ototóxico de los tratamientos quimioterápicos, la exposición a ruido o el mal entendimiento del lenguaje, especialmente en ambientes ruidosos. Se pretende destacar la importancia de la exploración audiométrica en altas frecuencias, con el fin de que se convierta en una herramienta habitual en la exploración audiológica.

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COMUNICACIÓN BREVE

Audiometría con extensión en altas frecuencias (9.000-20.000 Hz). Utilidad en el diagnóstico audiológico

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PALABRAS CLAVE
Audiometría con extensión en altas frecuencias;
Hipoacusia;
Tinnitus;
Presbiacusia;
Cisplatino

Resumen La detección precoz y el tratamiento adecuado de la hipoacusia es fundamental para minimizar las consecuencias de la pérdida auditiva. Además de la audiometría convencional (125-8.000 Hz), disponemos de la audiometría con extensión en altas frecuencias (9.000 - 20.000 Hz), que puede ser de gran utilidad en el diagnóstico precoz de hipoacusia en ciertas patologías, como es el efecto ototóxico de los tratamientos quimioterápicos, la exposición a ruido o el mal entendimiento del lenguaje, especialmente en ambientes ruidosos. Aquí se presentan 11 casos clínicos en los que la audiometría con extensión en altas frecuencias ha ayudado en la detección precoz de la hipoacusia en diversas patologías, a pesar de tener una audiometría normal en frecuencias convencionales. Se pretende así destacar la importancia de la exploración audiométrica en altas frecuencias, con el fin de que se convierta en una herramienta habitual en la exploración audiológica.

KEYWORDS
Extended high-frequency audiometry;
Hearing loss;
Tinnitus;
Presbycusis;
Cisplatin

Extended high-frequency audiometry (9,000-20,000 hz). Usefulness in audiological diagnosis

Abstract Early detection and appropriate treatment of hearing loss are essential to minimise the consequences of hearing loss. In addition to conventional audiometry (125-8,000 Hz), extended high-frequency audiometry (9,000-20,000 Hz) is available. This type of audiometry may be useful in early diagnosis of hearing loss in certain conditions, such as the ototoxic effect of cisplatin-based treatment, noise exposure or oral misunderstanding, especially in noisy environments. Eleven examples are shown in which extended high-frequency audiometry has been

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useful in early detection of hearing loss, despite the subject having a normal conventional audiometry. The goal of the present paper was to highlight the importance of the extended high-frequency audiometry examination for it to become a standard tool in routine audiological examinations.

Introducción

Se conocen muchos factores que pueden afectar a la audición como son la edad, la exposición a ruido o la toma de fármacos potencialmente ototóxicos. Tanto la detección precoz de la hipoacusia, como una intervención temprana, son fundamentales para minimizar las posibles consecuencias de la pérdida auditiva.

La valoración auditiva se realiza mediante la audiometría tonal convencional (125-8.000 Hz). No obstante, el oído humano posee un rango auditivo que alcanza hasta los 20.000 Hz. A las frecuencias comprendidas entre 9.000 y 20.000 Hz se les denomina *extended-high frequencies* en la literatura internacional. En castellano no existe un término equivalente definido, siendo denominadas por los distintos autores como *altas frecuencias*, *ultra-altas frecuencias* o *extensión en altas frecuencias* (EAF), siendo este último término el que vamos utilizar para referirnos a ellas.

La implicación de la EAF en la patología auditiva es múltiple. Pueden influir en la localización del sonido[1] y en el entendimiento del lenguaje, especialmente en ambientes ruidosos[2,3]. También se ha relacionado con la presbiacusia, la ototoxicidad y el trauma acústico. La capacidad de oír va disminuyendo con la edad, empezando esta pérdida en las frecuencias más altas y extendiéndose de forma progresiva hacia las frecuencias más bajas. De esta forma la EAF adquiere una especial importancia en la presbiacusia, como método de detección precoz de la misma.

La audiometría con EAF ha alcanzado un papel importante en la monitorización del efecto ototóxico de fármacos como el cisplatino, que produce una pérdida de audición inicial en EAF, afectando posteriormente a las frecuencias convencionales[4]. Sin embargo, aún está en discusión la utilidad de la audiometría con EAF frente a las frecuencias convencionales en la detección precoz del trauma acústico[5–8].

Recientemente se han publicado umbrales de audición de referencia distribuidos por grupos de edad tanto en frecuencias convencionales[9], como en EAF[10,11]. Estos valores nos permiten comparar la audición de un sujeto con el estándar de una población otológicamente normal, y establecer en qué grado su audición se aleja de la normalidad en función del percentil. De esta forma podemos valorar pacientes en tratamiento con quimioterápicos o expuestos a ruido que refieren pérdida de audición y de los que no disponemos de una audiometría previa.

El objetivo del presente trabajo es destacar la importancia de la audiometría en EAF, con el fin de que se convierta en una herramienta habitual en la exploración audiológica. Para ello presentamos una serie de casos clínicos en los que esta audiometría ha ayudado a la detección precoz de diversas patologías.

Métodos

Sujetos

Se han recogido los datos de 11 sujetos que acudieron a la consulta con sospecha de patología auditiva, en los que la audiometría en frecuencias convencionales fue normal, y a los que se les realizó una audiometría en EAF (tabla 1). Los pacientes seleccionados presentaban distintas patologías que pueden causar pérdida de audición a lo largo de la evolución de la enfermedad.

Instrumental y procedimiento

A todos los sujetos seleccionados se les realizó una audiometría tonal liminar por vía aérea para determinar el umbral de audición en las distintas frecuencias (125-20.000 Hz). Los resultados audiométricos obtenidos fueron comparados con los valores de normalidad para la población española publicados previamente en frecuencias convencionales[9] y en EAF[10].

Para la audiometría en frecuencias convencionales (125 a 8.000 Hz) se utilizó un audiómetro clínico Madsen Orbiter 922 y unos auriculares supra-aurales Telephonics TDH-39. La audiometría con EAF (9.000-20.000 Hz) se realizó con el mismo audiómetro y auriculares circumaurales Koss HV/1A. Todo el material audiométrico se calibró de acuerdo a las recomendaciones del fabricante y la normativa ISO 389-1[12] e IEC 60645-1[13]. Los transductores se calibraron de acuerdo a la ISO 389-1[12].

La audiometría se llevó a cabo de forma manual por personal entrenado, de acuerdo con la norma ISO 8253-1[14], dentro de una cabina sonoamortiguada. Los umbrales auditivos se determinaron de acuerdo al método ascendente establecido en la norma ISO 8253-1[14]. Los umbrales en las frecuencias convencionales fueron calculados en dB *Hearing Level* (dB HL), y los umbrales en EAF en dB *Sound Pressure Level* (dB SPL).

Resultados

En la tabla 1 se resumen las características de los sujetos a los que se les realizó la audiometría en frecuencias convencionales y en EAF.

Tabla 1 Sujetos a los que se les realizó audiometría con extensión en altas frecuencias

N	Edad	Sexo	Patología
1	24	H	Enfermedad de Fabry
2	26	H	Tinnitus tras minoxidil
3	20	M	Ca de cavum tratado con RT
4	21	H	Músico rock
5	26	H	Ca nasosinusal tratado con RT + cisplatino
6	39	H	No entiende en ambientes con ruido
7	38	H	Sospecha de hipoacusia genética
8	33	H	Hipoacusia fluctuante
9	39	M	Sospecha de hipoacusia autoinmune
10	49	H	Tinnitus
11	45	M	Tratamiento con ciclofosfamida + MTX + 5-FU

Ca: carcinoma; FU: fluorouracilo; H: hombre; M: mujer; MTX: metotrexato; RT: radioterapia.

Los casos 1, 2, 3 presentaban una audición normal hasta 8.000 Hz, con caída por debajo del percentil 95 (P95) para su grupo de edad (20-29 años) en las frecuencias a partir de 9.000 Hz (fig. 1).

El caso 4, músico de un grupo de rock durante 2 años, presentaba una audición por debajo del P95 solo en las frecuencias 9.000, 11.200 y 12.500 Hz (fig. 1). Las frecuencias donde más se alejaba de la mediana fueron 12.000 y 16.000 Hz.

El caso 5 es el de una mujer de 26 años con un carcinoma nasosinusal, que había recibido tratamiento con radioterapia y 3 ciclos de cisplatino hacía un año, y que presentaba una audición por debajo del P95 a partir de 4.000 Hz (fig. 1).

El caso 6, que refería dificultad de entendimiento en ambientes con ruido, presentaba una audición muy cercana a la mediana para su grupo de edad (30-39 años), con una caída por debajo del P95 en las frecuencias a partir de 14.000 Hz (fig. 2).

Los casos 7, 8 y 9 presentaban una audición por debajo del P95 a partir de 9.000, 8.000 y 4.000 Hz respectivamente (fig. 2).

El caso 10 refería acúfeno sin hipoacusia. La audiometría reflejaba una audición por debajo del P95 para su grupo de edad (40-49 años) a partir de 9.000 Hz, estando la audición en todas las frecuencias convencionales muy cercana a la mediana para su grupo de edad (fig. 3).

El caso 11, un hombre de 45 años que había recibido tratamiento con ciclofosfamida, metotrexato y 5-fluorouracilo, presentaba una audición por debajo del P95 a partir de 9.000 Hz, siendo la audiometría en frecuencias convencionales normal, aunque en 500 y 2.000 Hz está muy cercana al P95 (fig. 3).

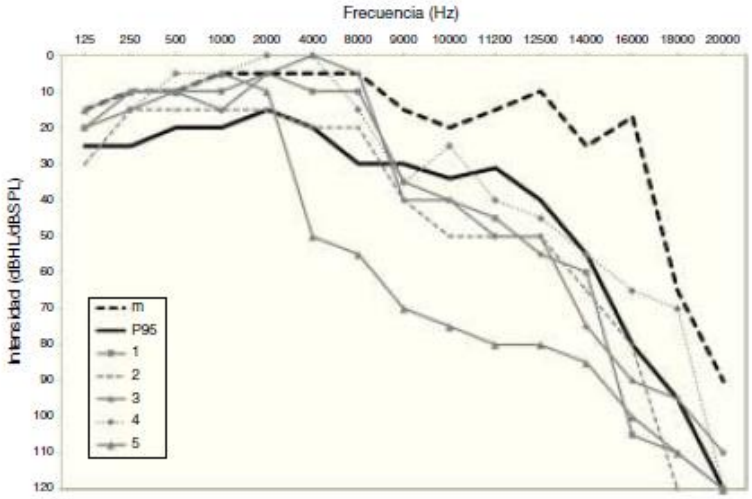

Figura 1 Audiometría de los sujetos 1, 2, 3, 4 y 5 comparados con la mediana (m) y el percentil 95 (P95) para el grupo de edad de 20-29 años.

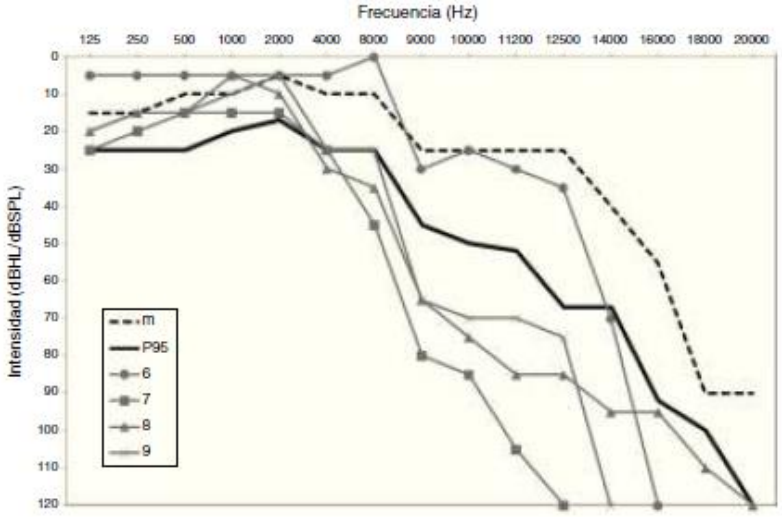

Figura 2 Audiometría de los sujetos 6, 7, 8 y 9 comparados con la mediana (m) y el percentil 95 (P95) para el grupo de edad de 30-39 años.

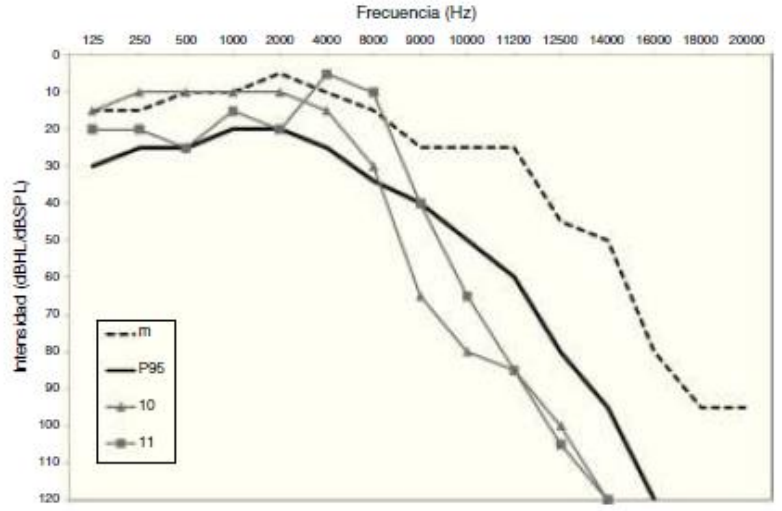

Figura 3 Audiometría de los sujetos 10 y 11 comparados con la mediana (m) y el percentil 95 (P95) para el grupo de edad de 40-49 años.

Discusión

Ciertas patologías sistémicas pueden producir hipoacusia neurosensorial, la cual puede ser detectada precozmente al realizar una audiometría con EAF. La enfermedad de Fabry es una enfermedad de almacenamiento lisosómico hereditaria ligada al cromosoma X. Dentro de la clínica que produce esta enfermedad se encuentra la hipoacusia neurosensorial. En el caso 1 el sujeto no manifestaba hipoacusia, con una audiometría en frecuencias convencionales normal, lo que nos podría llevar a pensar que este sujeto no presentaba afectación auditiva. Sin embargo, al realizar la audiometría con EAF se vio una pérdida importante en todas las frecuencias entre 9.000 y 20.000 Hz.

Muchos pacientes consultan por tinnitus, sin referir pérdida de audición, como son los casos 2 y 10. En el caso 2 el sujeto refería tinnitus y mareo tras el uso de minoxidil. La audiometría en frecuencias convencionales fue normal, pero

en la audiometría con EAF los umbrales de audición estaban muy por debajo de la normalidad, pérdida que podría justificar el tinnitus.

La radioterapia en la región de la cabeza es otra causa de hipoacusia neurosensorial. En el caso 3, una paciente tratada con radioterapia por un carcinoma de cavum, presentó una pérdida de audición solo detectable en la audiometría con EAF, especialmente en las frecuencias entre 9.000 y 16.000 Hz.

El caso 4 representa a un sujeto expuesto a música a un volumen alto, y donde se puede ver una pérdida de audición en EAF, especialmente en las frecuencias comprendidas entre 11.200 y 14.000 Hz, alejándose más de la mediana en 12.000 y 16.000 Hz.

Algunos autores han encontrado que el trauma acústico afecta a las frecuencias 3.000-6.000 Hz y también de forma considerable a la EAF[5], especialmente en 14.000 Hz[6] y 16.000 Hz[7]. La audiometría con EAF es más sensible que la audiometría convencional, especialmente en sujetos jóvenes[7], aunque no todos los autores creen que la audiometría con EAF aporte información adicional[8]. Por lo tanto, no disponemos aún de datos concluyentes para establecer la utilidad de la audiometría con EAF en la detección precoz de la hipoacusia inducida por ruido.

Es bien conocida la utilidad de la audiometría con EAF en la detección precoz de la hipoacusia en sujetos sometidos a tratamientos quimioterápicos derivados del platino, siendo el cisplatino el que presenta mayor riesgo de desarrollar efectos ototóxicos. Otros quimioterápicos como el metotrexato y la ciclofosfamida también son conocidos por producir hipoacusia neurosensorial. En el caso 5 la paciente fue tratada con cisplatino y en su audiometría se puede apreciar una gran pérdida de audición, ya detectable en las frecuencias convencionales (4.000 Hz). Hay que señalar que, aunque el umbral de audición está muy disminuido, la audición se mantiene en todas las frecuencias hasta 20.000 Hz, algo que ocurre en los sujetos más jóvenes, que conservan su audición hasta frecuencias muy altas, aunque esté por debajo de la normalidad (fig. 1). En el caso 11 solo se puede ver la afectación de la audición al realizar la audiometría en EAF.

Las frecuencias comprendidas entre 500 y 4.000 Hz se han considerado tradicionalmente como las más importantes para el entendimiento de la palabra. El rango de frecuencias conversacionales de la voz humana está entre 250 y 3.000 Hz; si bien algunos fonemas se encuentran situados entre los 4.000 y los 8.000 Hz, incluso en frecuencias más altas, especialmente en las consonantes fricativas[3]. El mal entendimiento de la palabra en ambientes ruidosos, como en el caso 6, podría estar justificado por la pérdida de audición en las frecuencias más altas, en este caso en las frecuencias por encima de 14.000 Hz.

Muchos casos con sospecha de sordera de origen genético o autoinmune se pueden beneficiar de la realización de una audiometría con EAF para detectar la hipoacusia de forma precoz. En los casos 7, 8 y 9 se observa esta pérdida de audición en EAF, con más o menos afectación de las frecuencias convencionales más agudas.

Por todas estas razones, la audiometría con EAF puede ser de gran utilidad en la detección precoz de la hipoacusia neurosensorial, y su realización se debería instaurar en la práctica clínica habitual con el fin de ampliar el estudio del rango auditivo de los pacientes.

Conflicto de intereses

Los autores declaran no tener ningún conflicto de intereses.

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Anexo 5:

“Intratympanic gadolinium MRI can support the role of endolymphatic hydrops in immune-mediated inner ear disease.”

El objetivo de este estudio fue evaluar la presencia de hídrops endolinfático en pacientes con una enfermedad inmunomediada del oído interno. Este estudio confirma la presencia de hídrops endolinfático en pacientes con EIOI. La ausencia virtual de hídrops en pacientes con EIOI secundaria es destacable en esta muestra poblacional de pacientes con EIOI sin embargo, conclusiones específicas al respecto no se pueden obtener con este estudio precisando de una muestra de mayor tamaño.

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CAN POSITRON EMISSION TOMOGRAPHY SUPPORT THE CHARACTERIZATION OF IMMUNE-MEDIATED INNER EAR DISEASE?

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Short title: PET-CT IN THE IMIED

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CAN POSITRON EMISSION TOMOGRAPHY SUPPORT THE CHARACTERIZATION OF IMMUNE-MEDIATED INNER EAR DISEASE?

ABSTRACT

Introduction:

To evaluate the utility of positron emission tomography -computed tomography (PET/CT) as an imaging tool in the characterization of immune-mediated inner ear disease (IMIED), providing measurements of the inner ear region activity as well as possible involvement of other organs.

Material and Methods:

Study of 28 patients with IMIED and 4 sex-matched and age-matched control subjects without any history of autoimmune inner ear disease. Eighteen patients were considered as suffering from primary form of IMIED and 10 patients from secondary. PET/CT with 18F-FDG were performed to assess systemic involvement as well as inner ear region activity. Interpretation of PET/CT scans was performed independently by two nuclear medicine physicians blinded to clinical history. In order to assess inter-rater agreement before performing the analysis of the inner ear, different Bland&Altman plots and the intraclass correlation coefficients were estimated.

Results:

Different metabolically active foci findings were reported in 13 patients. Four patients diagnosed as primary IMIED showed thyroid and aorta activity. Regarding the inner-ear semicuantitative analysis, the inter-rater agreement was not high enough. Comparisons between groups, performed through Mann-Whitney test or Kruskal-Wallis test, showed no differences.

Conclusions:

The study has proven 18F-FDG-PET/CT can be an important tool in the evaluation of IMIED since it can support the characterization of this entity providing the diagnosis of

unknown or underestimated secondary IMIED. Nevertheless, we consider PET is not an adequate tool in the approach to the inner ear since the little size and volume of the cochlea make the assessment very difficult.

Keywords: immune-mediated hearing loss, positron emission tomography, inner ear, systemic autoimmune disease, FDG

¿PUEDE LA TOMOGRAFIA POR EMISIÓN DE POSITRONES AYUDAR EN LA CARACTERIZACIÓN DE LA ENFERMEDAD INMUNOMEDIADA DEL OIDO INTERNO PRIMARIA?

RESUMEN

Introducción

Evaluar la utilidad de la PET-TC con 18F-FDG en la caracterización de la enfermedad inmunomediada del oído interno primaria (EIOI) aportando datos que ayuden a valorar la actividad inflamatoria y la existencia o ausencia de enfermedad sistémica asociada.

Material y métodos

Estudio prospectivo sobre 28 pacientes con sospecha de EIOI o EIOI primaria diagnosticada y controles sin enfermedad otológica conocida con PET FDG realizado por otro motivo. A todos se les realizó imagen selectiva de cráneo y estudio estándar.

La interpretación del resultado del PET fue realizada por dos médicos nucleares ciegos a la clínica del paciente. Para valorar la reproductibilidad de las medidas se realizaron análisis Bland&Altman y correlación de coeficientes interclase.

Resultados

Se encontraron hallazgos sospechosos de afectación sistémica en 13 pacientes. Cuatro de ellos correspondieron a pacientes diagnosticados previamente de EIOI primaria que mostraron actividad inflamatoria (tiroidea y aórtica). En cuanto al análisis semicuantitativo de la actividad metabólica en el oído interno, la variabilidad interobservador fue muy alta y no fue posible establecer diferencias adecuadas entre grupos.

Conclusiones

Este estudio demuestra que el PET-TC con 18F-FDG podría tener un papel en la evaluación de pacientes con sospecha de EIOI primaria descartando la presencia de datos que sugieran inflamación sistémica. Consideramos que no es adecuado tratar de cuantificar la actividad metabólica del oído interno probablemente por el pequeño tamaño del mismo.

Palabras clave: Enfermedad inmunomediada del oído interno, PET, oído interno, enfermedad autoinmune sistémica, FDG

INTRODUCTION

Immune-mediated inner ear disease (IMIED) is an accepted clinical syndrome presenting as rapidly progressive sensorineural hearing loss that is responsive to steroids (1). Initially it may present as a sudden unilateral disease, often progressing to bilateral deafness or sensorineural hearing loss, occasionally associated with vestibular symptoms. Idiopathic sudden sensorineural hearing loss (sudden deafness) and Meniere's disease can share the clinical picture and mimic IMIED. Some forms of both entities are thought to be due to an autoimmune process (2, 3) (Table 1).

The syndrome refers to a pathology restricted to the ear (primary IMIED) or to multisystemic, organ-nonspecific autoimmune diseases involving the inner ear (secondary IMIED) (4). Primary IMIED is a rare disorder and it represents a challenge for otologists because of the lack of a definitive diagnostic test (5).

Since IMIED is one of the few inner ear disorders reversible to medical therapy, many attempts, mainly in primary forms, in order to early diagnosis, have been made. Thus, high risk profile (6) and MRI studies in patients affected by sudden sensorineural hearing loss have been suggested (7).

Positron emission tomography (PET/CT) has become an excellent tool to assess disease activity and prognosis in some systemic autoimmune diseases like systemic lupus erythematosus (SLE). By targeting the increased glucose uptake of infiltrating granulocytes, tissue macrophages and activated lymphocytes, positron emission tomography with fluorine-18 fluorodeoxyglucose ((18) F)FDG PET/CT) has been shown to visualize large concentrations of these cells in lymphoid organs where antigen presentation and lymphocyte activation occur (8). Because of its good performance in the field of inflammatory disease, PET/CT has been introduced as a diagnostic tool in the algorithms of different multisystemic inflammatory processes (9).

A pilot study reported that FDG can be used in PET to assess disease activity in patients with IMIED (10). The aim of the present study is to validate the role of PET/CT in the characterization of primary and secondary IMIED, providing measurements of the inner ear region activity as well as possible involvement of other organs. This analysis could be remarkable in primary IMIED patients, who show negative serological tests, making difficult a nearly diagnosis and prompt treatment.

MATERIAL AND METHODS

Twenty eight patients affected by IMIED, 20 women and 8 men (mean age 43.7 years; range 15-72 years) assisted in the Department of Otorhinolaryngology from January 2013 to November 2016, have been included in the study. Four sex- matched and age-matched without any history of autoimmune inner ear disease or active inflammatory disease or cancer (referred for neurological PET) were considered as control subjects. Exclusion criteria: neoplasm, active infections, vasculitis, or active inflammatory processes in the temporal bone region. Eighteen patients were considered as primary IMIED and 10 patients were included in the secondary IMIED group (Table 2). Informed consent was obtained from all patients and controls. The study was approved by the Clinical Research and Ethics Committee of our institution (PI 15/16, Acta 04.16). Patients were studied according to our diagnostic protocol (Figure 1). Most patients had been treated with high-dose corticosteroid therapy (Methylprednisolone or prednisolone, 1 mg/kg/day, intratympanic Methylprednisolone and Methotrexate, 10.0–20.0 mg/week) before PET scanning. None had hyperglycemia or diabetes. PET/CT images were obtained using a dedicated PET/CT system (Biograph 6, Siemens Medical Systems, Knoxville, TN, USA). Patients were requested to fast for 6 hour before the study. Acquisition began 60 minutes after the intravenous injection of 370 MBq of 18F-FDG. Image protocol included a 1 BED selective image of the base of skull (10 minutes/BED) followed by a standard PET/CT whole body study (4 minutes/BED). Images were reconstructed with a 168x168 matrix using the ordered subset expectation maximum iterative reconstruction algorithm.

The PET scans were interpreted visually and semiquantitatively.Two analyses were performed. The first consisted of assessing the PET scans in order to rule out any organ inflammation. The second looked for activity in the inner ear (cochlea) that was greater than background. These observations were then compared among the individual study patients and the control subjects.

In order to asses metabolic activity in the inner ear Region of Interest (ROI) were drawn in PET image at CT slice in which more cochlear membrane could be depicted and avoiding physiological brain uptake. An additional background ROI for each patient was placed at sphenoid sinus. (Figure 2)

Two nuclear medicine physicians blinded to the diagnoses and identities of patients reviewed the PET images independently.

Statistical Analysis

In order to assess inter-rater agreement before performing the analysis of the inner ear, different Bland&Altman plots (11) were drew, according to different measures: right ear (RE), left ear (LE), background (B), ratio RE/B and ratio LE/B. The intraclass correlation coefficients (ICCs) (12) were also estimated by means of two- way random-effects models. Comparisons between groups were performed through Mann-Whitney test or Kruskal-Wallis test. The software used was Stata v14.1 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

RESULTS

Ten patients had been treated with corticosteroids (oral and/or intratympanic) associated or not with immunosuppressive drugs 3 months before performing the PET scan and 8 were receiving such as treatment during the exploration. PET showed no activity in 15 patients (10 primary IMIED and 5 secondary IMIED). Different organs activity was reported in the rest of patients (Table 3). Two patients with Waldeyer´s ring activity were diagnosed of upper tract respiratory infection. Vertebral hemangioma and spine disc herniation (slipped disc) caused lumbar spine activity. Prostate activity was associated to benign prostate hyperplasia.

Involvement of thyroid and aorta were thought to be due to systemic autoimmune disease. In the primary IMIED group, 2 patients were diagnosed of autoimmune thyroiditis and Cogan´s syndrome was considered in other 2 patients (Figure 3).

Accordingly 4 patients changed the diagnosis to secondary IMIED following PET. Inner ear analysis in the cochlea is shown in Table 4. Measuring agreement is shown in Bland & Altman plots (Figure 4) (Table 5).

The Intraclass Correlation Coefficients (ICCs) ranged from .42 for background (fair) to .82 for right ear (excellent) (13) (Table 6). No significant differences could be observed

when compared the three groups (primary patients, secondary patients and control subjects).

DISCUSSION

Immune-mediated inner ear disease represents a diagnostic and therapeutic challenge given its lack of reliable diagnostic criteria and varied clinical presentation; IMIED can mimic other disorders of the cochleovestibular system. A significant amount of work has gone into identifying serological tests to identify IMIED patients; however to date none has proven sufficiently accurate. Therefore the clinical diagnosis made by demonstration of a beneficial response to immunosuppressive therapy is mandatory. PET could be useful for evaluating inflammatory, autoimmune or rheumatic disorders. A pilot study reported that PET imaging was abnormal in the inner ear region in four of five patients with active disease (14). However, the study does not report measurements of the inner ear activity. In the present study we show measurements activity inside the cochlea in order to compare primary patients with secondary patients and control subjects. Nevertheless the inter-rater agreement was not high enough. Taking into account that the volume of the inner ear ranges between 0.14ml and 0.18ml (15) the measurement of the activity of such as little area is very difficult and it can vary between different observers. Despite having acquired selective images for 10 minutes BED position, and considering the limitation of our small cohort of patients, PET/CT sensibility does not seem enough to detect metabolic changes in inner ear. Other factors influencing the capability of PET to detect these changes may be the proximity of the ROIs to brain cortex uptake and a pixel size of 4mm, that prone to partial volume effect. Even this result was predictable; the only reference about IMIED and PET concludes that FDG-PET is able to measure inner ear metabolic activity (14).

The lack of statistically differences among the groups could be justified by this fact. The presence of other organ with high activity could support the diagnosis of secondary IMIED, initially reported with negative serological markers and diagnosed as primary IMIED. Immunosuppressive therapy before or during the evaluation may have caused a lesser organ involvement and no activity in some patients.

The present study has proven PET may be an important imaging tool in the evaluation of IMIED since it can support the characterization of this entity, mainly in the diagnosis of non suspected secondary IMIED in former examination. Accordingly we propose our diagnostic algorithm in the evaluation of IMIED. Taking into consideration that IMIED is a chronic disorder, in the long-term follow-up we may diagnose more patients affected by secondary IMIED by means of the diagnostic protocol suggested in the study. Nevertheless, we consider PET is not very useful up-to-date in the approach to the inner ear since the little size and volume of the cochlea make the assessment of activity very difficult. Pixel size and proximity to cortex brain hamper the metabolic assessment of the inner ear.

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FIGURE LEGENDS

Figure 1. Stepwise algorithm for the approach to a patient with suspected IMIED. *Negative PET in Secondary IMIED may be due to inactive disease and/or immunosuppressive therapy.

Figure 2. Transaxial view of (A) CT (B) fused PET/CT, (C) PET images showing the ROI 1 placed at the inner ear level in which more cochlear membranes can be depicted and ROI2 placed at the sphenoid sinus to assess background activity level. (D) Maximum intensity projection.

Figure 3. Coronal view of (A) PET (B) fused PET/CT images showing increased uptake in the aortic wall in a patient with suspected IMIED. Cogan´s syndrome was considered after PET result.

Figure 4. Bland & Altman plots according to different measures: right ear (RE), left ear (LE), background (B), ratio RE/B and ratio LE/B.

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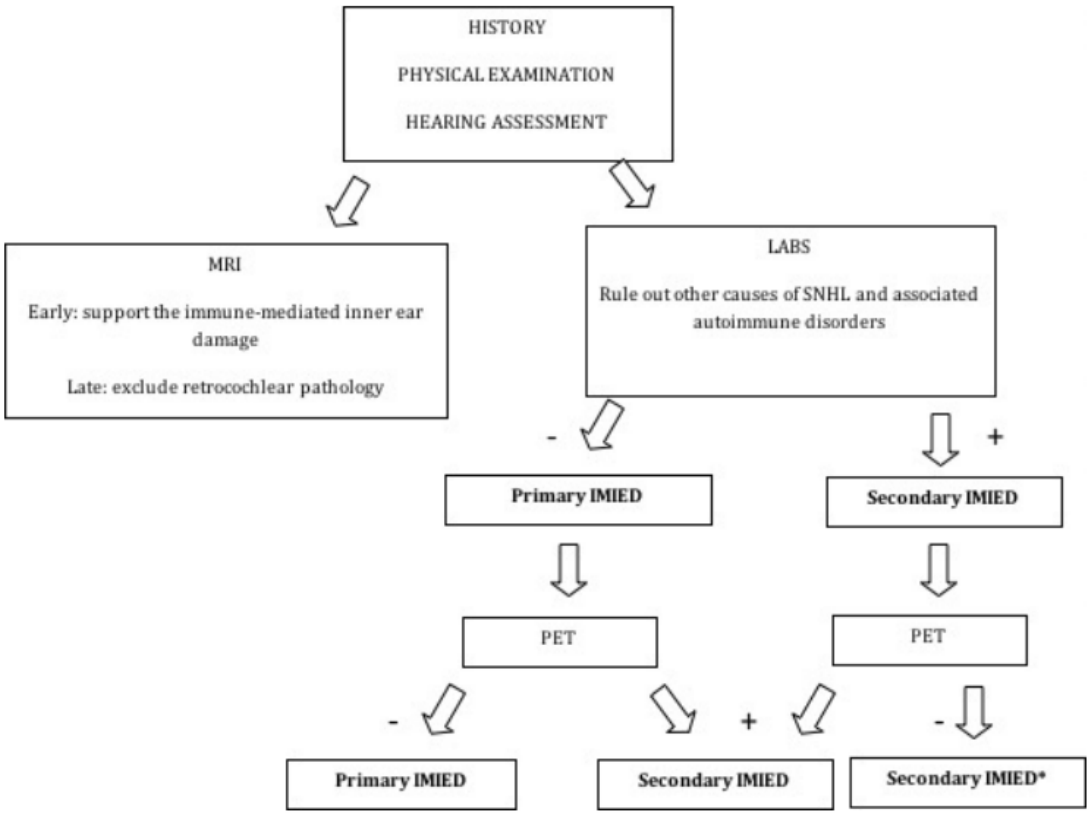
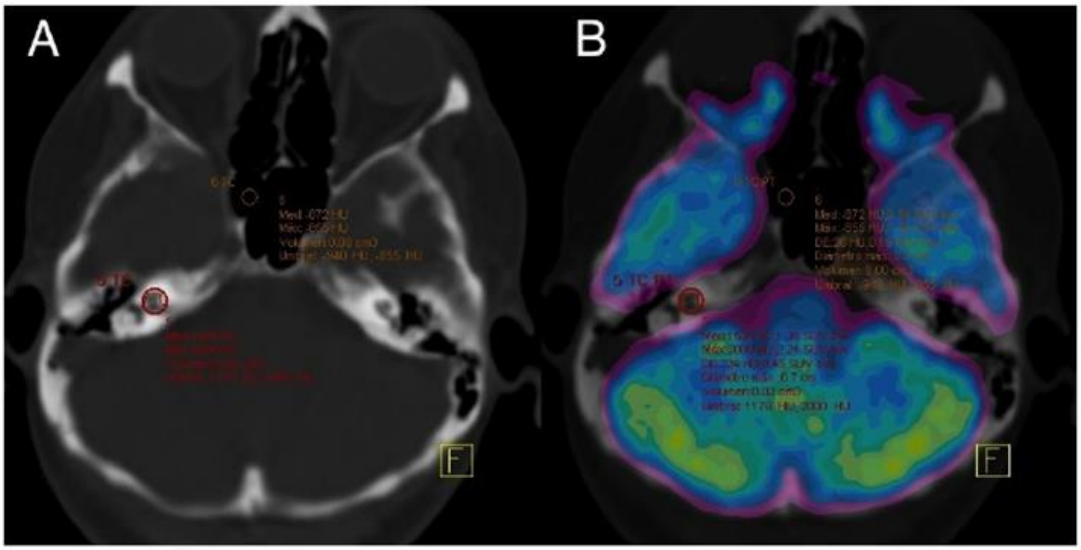

HISTORY
PHYSICAL EXAMINATION
HEARING ASSESSMENT
MRI
Early: support the immune-mediated inner ear damage
Late: exclude retrocochlear pathology
LABS
Rule out other causes of SNHL and associated autoimmune disorders
-
+
Primary IMIED
Secondary IMIED
PET
PET
-
+
-
Primary IMIED
Secondary IMIED
Secondary IMIED*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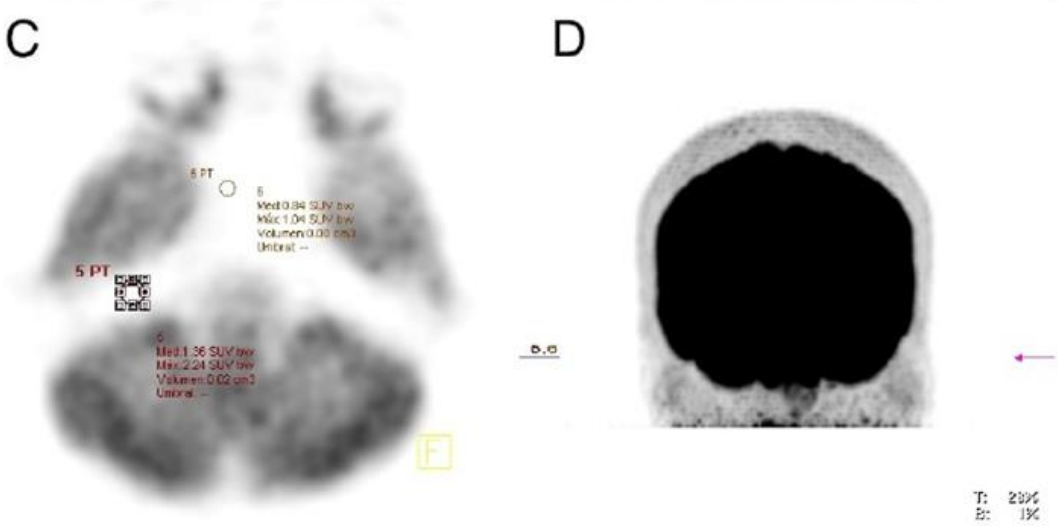
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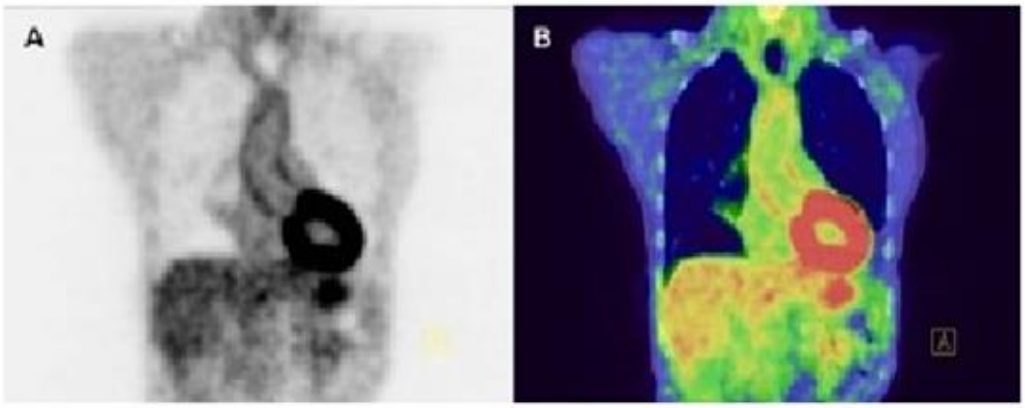
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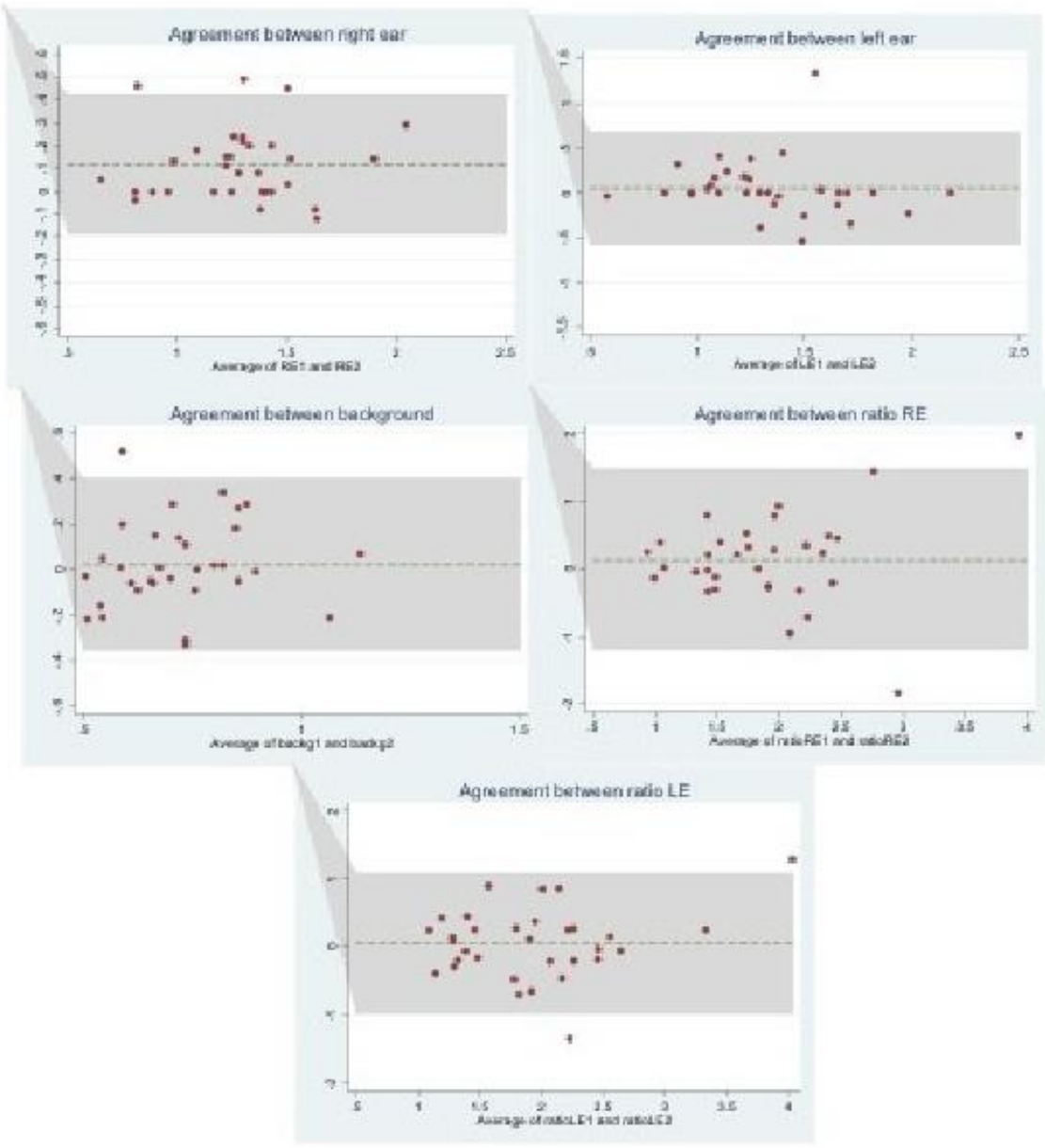
Agreement between right ear
Agreement between left ear
Agreement between background
Agreement between ratio RE
Agreement between ratio LE

Table 1. Clinical manifestations of IMIED. Sensorineural hearing loss (SNHL) is responsive to corticosteroids.

Asymmetric bilateral rapidly progressive SNHL (weeks or months).
Bilateral sudden SNHL (hours to days).
Recurrent sudden SNHL (more than 2 episodes in one year).
Fluctuating SNHL in one ear following inner ear damage in the opposite ear (CMV infection, inner or middle ear surgery, sudden SNHL) (days to years after the event).
Bilateral Meniere´s disease.

Table 2. Systemic autoimmune diseases in secondary IMIED.

Antiphospholipid syndrome	1
Antiphospholipid syndrome + Sjogren syndrome	1
Sjogren syndrome	1
Autoimmune thyroiditis	5
Autoimmune thyroiditis + autoimmune encephalitis	1
Connective disease + celiac disease	1

Table 3. Patients included in the study. *One patient affected by secondary IMIED showed multiple activity. N-number of patients. W-women. M-men.

Primary IMIED	N patients	sex	age	No activity	thyroid	aorta	Waldeyer ring	spine	lung	prostate
	18	10 w 8 m	41.8 15-72	10	2	2	2	2	1	1
Secondary IMIED	N patients	sex	age	No activity	thyroid	aorta	adrenal gland	pituitary gland	uterus	perineum
	10	10 w	47.1 26-58	5	3	2*	1*	1*	1*	1*

group	n	Right ear (RE)	Left ear (LE)	Background (B)	Ratio RE/B	Ratio LE/B
Control	4	1.37 (0.40)	1.377 (0.70)	0.68 (0.17)	1.99 (0.33)	1.95 (0.74)
Primary IMIED	18	1.35 (0.34)	1.32 (0.34)	0.75 (0.19)	1.96 (0.96)	1.91 (0.91)
Secondary IMIED	10	1.30 (0.26)	1.42 (0.19)	0.71 (018)	1.91 (0.52)	2.05 (0.39)

A

group	n	Right ear (RE)	Left ear (LE)	Background (B)	Ratio RE/B	Ratio LE/B
Control	4	1.12 (0.22)	0.92 (0.24)	0.57 (0.16)	2.19 (1.15)	1.72 (0.70)
Primary IMIED	18	1.22 (0.34)	1.34 (0.42)	0.75 (0.17)	1.67 (0.52)	1.84 (0.66)
Secondary IMIED	10	1.23 (0.29)	1.41 (0.33)	0.67 (0.12)	1.89 (0.59)	2.15 (0.59)

B

Table 4. Inner ear measurements performed by each consultant (A and B). Mean and Standard deviation ( ) are shown. n- number of patients.

Table 5. Bland & Altman analysis.

Batplot	Mean difference	Limits of agreement	Averages
Agreement between right ear (RE)	.115937500318978	(-.1873664026340678,.4192414032720238)	0.655 and 2.045
Agreement between left ear (LE)	.0525000012712553	(-.5761488511522573,.681148853694768)	0.580 and 2.180
Agreement between background (B)	.0234374997671694	(-.3528653545342372,.399740354068576l)	0.505 and 1.135
Agreement between ratio RE/B	.1328392176656053	(-1.198995743249829,1.464674178581039)	0.940 and 3.938
Agreement between ratio LE/B	.0538094497751445	(-.9679355200363946,1.075554419586684)	1.093 and 4.031

Table 6. Intraclass Correlation Coefficients (ICCs)

	ICC	(95%	Conf. Interval)
Right ear (RE)	.8278208	.4837779	.9305282
Left ear (LE)	.6443895	.388539	.8085289
Background (B)	.4241236	.0922898	.6707279
Ratio RE/B	.549665	.2582356	.7504987
Ratio LE/B	.7249198	.5076572	.8555285

Less than 0.40—Poor.
Between 0.40 and 0.59—Fair.
Between 0.60 and 0.74—Good.
Between 0.75 and 1.00—Excellent.

Anexo 6

“Can positron emission tomography support the characterization of immune-mediated inner ear disease?” “¿Puede la tomografía por emisión de positrones ayudar en la caracterización de la enfermedad inmunomediada del oído interno primaria?”

En este artículo se busca evaluar la utilidad de la PET-TC con 18F- FDG en la caracterización de la enfermedad inmunomediada del oído interno primaria (EIOI) aportando datos que ayuden a valorar la actividad inflamatoria y la existencia o ausencia de enfermedad sistémica asociada. Este estudio demuestra que el PET-TC con 18F-FDG podría tener un papel en la evaluación de pacientes con sospecha de EIOI primaria descartando la presencia de datos que sugieran inflamación sistémica. Consideramos que no es adecuado tratar de cuantificar la actividad metabólica del oído interno probablemente por el pequeño tamaño del mismo.

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CAN POSITRON EMISSION TOMOGRAPHY SUPPORT THE CHARACTERIZATION OF IMMUNE-MEDIATED INNER EAR DISEASE?

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Short title: PET-CT IN THE IMIED

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ABSTRACT

Introduction:

To evaluate the utility of positron emission tomography -computed tomography (PET/CT) as an imaging tool in the characterization of immune-mediated inner ear disease (IMIED), providing measurements of the inner ear region activity as well as possible involvement of other organs.

Material and Methods:

Study of 28 patients with IMIED and 4 sex-matched and age-matched control subjects without any history of autoimmune inner ear disease. Eighteen patients were considered as suffering from primary form of IMIED and 10 patients from secondary. PET/CT with 18F-FDG were performed to assess systemic involvement as well as inner ear region activity. Interpretation of PET/CT scans was performed independently by two nuclear medicine physicians blinded to clinical history. In order to assess inter-rater agreement before performing the analysis of the inner ear, different Bland&Altman plots and the intraclass correlation coefficients were estimated.

Results:

Different metabolically active foci findings were reported in 13 patients. Four patients diagnosed as primary IMIED showed thyroid and aorta activity. Regarding the inner-ear semicuantitative analysis, the inter-rater agreement was not high enough. Comparisons between groups, performed through Mann-Whitney test or Kruskal-Wallis test, showed no differences.

Conclusions:

The study has proven 18F-FDG-PET/CT can be an important tool in the evaluation of IMIED since it can support the characterization of this entity providing the diagnosis of

unknown or underestimated secondary IMIED. Nevertheless, we consider PET is not an adequate tool in the approach to the inner ear since the little size and volume of the cochlea make the assessment very difficult.

Keywords: immune-mediated hearing loss, positron emission tomography, inner ear, systemic autoimmune disease, FDG

¿PUEDE LA TOMOGRAFIA POR EMISIÓN DE POSITRONES AYUDAR EN LA CARACTERIZACIÓN DE LA ENFERMEDAD INMUNOMEDIADA DEL OIDO INTERNO PRIMARIA?

RESUMEN

Introducción

Evaluar la utilidad de la PET-TC con 18F-FDG en la caracterización de la enfermedad inmunomediada del oído interno primaria (EIOI) aportando datos que ayuden a valorar la actividad inflamatoria y la existencia o ausencia de enfermedad sistémica asociada.

Material y métodos

Estudio prospectivo sobre 28 pacientes con sospecha de EIOI o EIOI primaria diagnosticada y controles sin enfermedad otológica conocida con PET FDG realizado por otro motivo. A todos se les realizó imagen selectiva de cráneo y estudio estándar.

La interpretación del resultado del PET fue realizada por dos médicos nucleares ciegos a la clínica del paciente. Para valorar la reproductibilidad de las medidas se realizaron análisis Bland&Altman y correlación de coeficientes interclase.

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The PET scans were interpreted visually and semiquantitatively.Two analyses were performed. The first consisted of assessing the PET scans in order to rule out any organ inflammation. The second looked for activity in the inner ear (cochlea) that was greater than background. These observations were then compared among the individual study patients and the control subjects.

In order to asses metabolic activity in the inner ear Region of Interest (ROI) were drawn in PET image at CT slice in which more cochlear membrane could be depicted and avoiding physiological brain uptake. An additional background ROI for each patient was placed at sphenoid sinus. (Figure 2)

Two nuclear medicine physicians blinded to the diagnoses and identities of patients reviewed the PET images independently.

Statistical Analysis

In order to assess inter-rater agreement before performing the analysis of the inner ear, different Bland&Altman plots (11) were drew, according to different measures: right ear (RE), left ear (LE), background (B), ratio RE/B and ratio LE/B. The intraclass correlation coefficients (ICCs) (12) were also estimated by means of two- way random-effects models. Comparisons between groups were performed through Mann-Whitney test or Kruskal-Wallis test. The software used was Stata v14.1 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

RESULTS

Ten patients had been treated with corticosteroids (oral and/or intratympanic) associated or not with immunosuppressive drugs 3 months before performing the PET scan and 8 were receiving such as treatment during the exploration. PET showed no activity in 15 patients (10 primary IMIED and 5 secondary IMIED). Different organs activity was reported in the rest of patients (Table 3). Two patients with Waldeyer´s ring activity were diagnosed of upper tract respiratory infection. Vertebral hemangioma and spine disc herniation (slipped disc) caused lumbar spine activity. Prostate activity was associated to benign prostate hyperplasia.

Involvement of thyroid and aorta were thought to be due to systemic autoimmune disease. In the primary IMIED group, 2 patients were diagnosed of autoimmune thyroiditis and Cogan´s syndrome was considered in other 2 patients (Figure 3).

Accordingly 4 patients changed the diagnosis to secondary IMIED following PET. Inner ear analysis in the cochlea is shown in Table 4. Measuring agreement is shown in Bland & Altman plots (Figure 4) (Table 5).

The Intraclass Correlation Coefficients (ICCs) ranged from .42 for background (fair) to .82 for right ear (excellent) (13) (Table 6). No significant differences could be observed

when compared the three groups (primary patients, secondary patients and control subjects).

DISCUSSION

Immune-mediated inner ear disease represents a diagnostic and therapeutic challenge given its lack of reliable diagnostic criteria and varied clinical presentation; IMIED can mimic other disorders of the cochleovestibular system. A significant amount of work has gone into identifying serological tests to identify IMIED patients; however to date none has proven sufficiently accurate. Therefore the clinical diagnosis made by demonstration of a beneficial response to immunosuppressive therapy is mandatory. PET could be useful for evaluating inflammatory, autoimmune or rheumatic disorders. A pilot study reported that PET imaging was abnormal in the inner ear region in four of five patients with active disease (14). However, the study does not report measurements of the inner ear activity. In the present study we show measurements activity inside the cochlea in order to compare primary patients with secondary patients and control subjects. Nevertheless the inter-rater agreement was not high enough. Taking into account that the volume of the inner ear ranges between 0.14ml and 0.18ml (15) the measurement of the activity of such as little area is very difficult and it can vary between different observers. Despite having acquired selective images for 10 minutes BED position, and considering the limitation of our small cohort of patients, PET/CT sensibility does not seem enough to detect metabolic changes in inner ear. Other factors influencing the capability of PET to detect these changes may be the proximity of the ROIs to brain cortex uptake and a pixel size of 4mm, that prone to partial volume effect. Even this result was predictable; the only reference about IMIED and PET concludes that FDG-PET is able to measure inner ear metabolic activity (14).

The lack of statistically differences among the groups could be justified by this fact. The presence of other organ with high activity could support the diagnosis of secondary IMIED, initially reported with negative serological markers and diagnosed as primary IMIED. Immunosuppressive therapy before or during the evaluation may have caused a lesser organ involvement and no activity in some patients.

The present study has proven PET may be an important imaging tool in the evaluation of IMIED since it can support the characterization of this entity, mainly in the diagnosis of non suspected secondary IMIED in former examination. Accordingly we propose our diagnostic algorithm in the evaluation of IMIED. Taking into consideration that IMIED is a chronic disorder, in the long-term follow-up we may diagnose more patients affected by secondary IMIED by means of the diagnostic protocol suggested in the study. Nevertheless, we consider PET is not very useful up-to-date in the approach to the inner ear since the little size and volume of the cochlea make the assessment of activity very difficult. Pixel size and proximity to cortex brain hamper the metabolic assessment of the inner ear.

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FIGURE LEGENDS

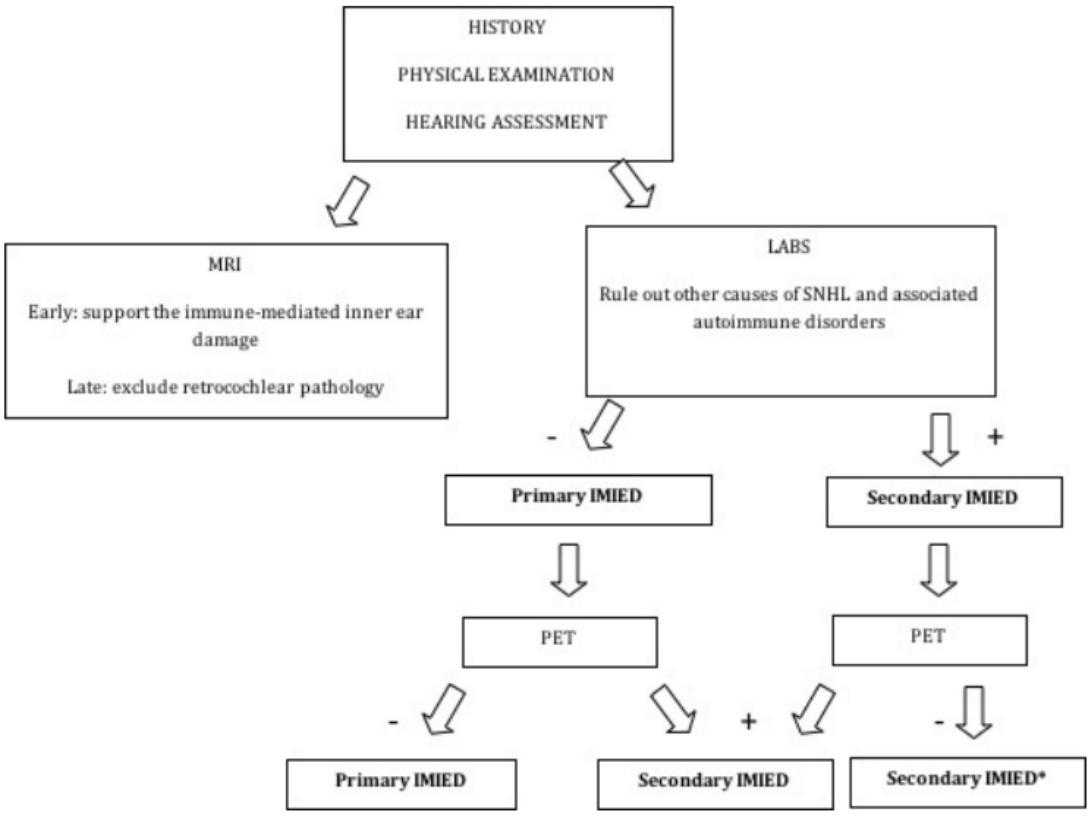
Figure 1. Stepwise algorithm for the approach to a patient with suspected IMIED. *Negative PET in Secondary IMIED may be due to inactive disease and/or immunosuppressive therapy.

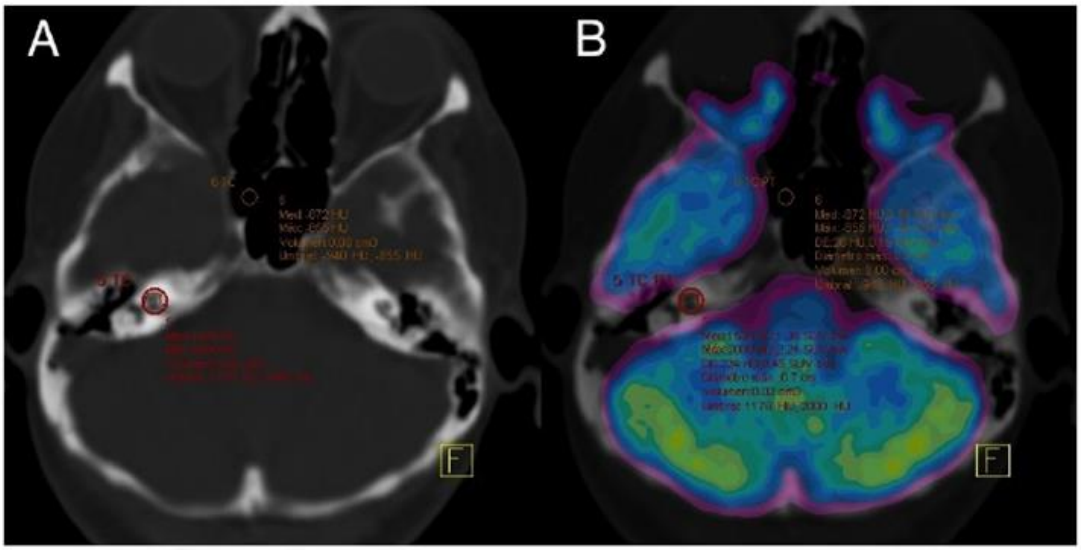
Figure 2. Transaxial view of (A) CT (B) fused PET/CT, (C) PET images showing the ROI 1 placed at the inner ear level in which more cochlear membranes can be depicted and ROI2 placed at the sphenoid sinus to assess background activity level. (D) Maximum intensity projection.

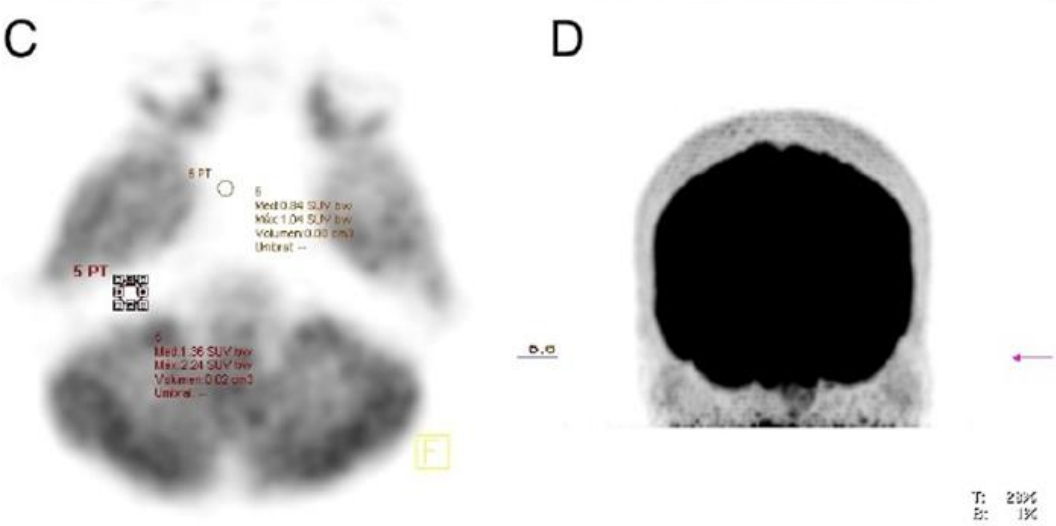
Figure 3. Coronal view of (A) PET (B) fused PET/CT images showing increased uptake in the aortic wall in a patient with suspected IMIED. Cogan´s syndrome was considered after PET result.

Figure 4. Bland & Altman plots according to different measures: right ear (RE), left ear (LE), background (B), ratio RE/B and ratio LE/B.

ACKNOWLEDGEMENTS: We thank Ana Royuela for the statistical analysis.


HISTORY
PHYSICAL EXAMINATION
HEARING ASSESSMENT
MRI
Early: support the immune-mediated inner ear damage
Late: exclude retrocochlear pathology
LABS
Rule out other causes of SNHL and associated autoimmune disorders
-
+
Primary IMIED
Secondary IMIED
PET
PET
-
+
-
Primary IMIED
Secondary IMIED
Secondary IMIED*


A
B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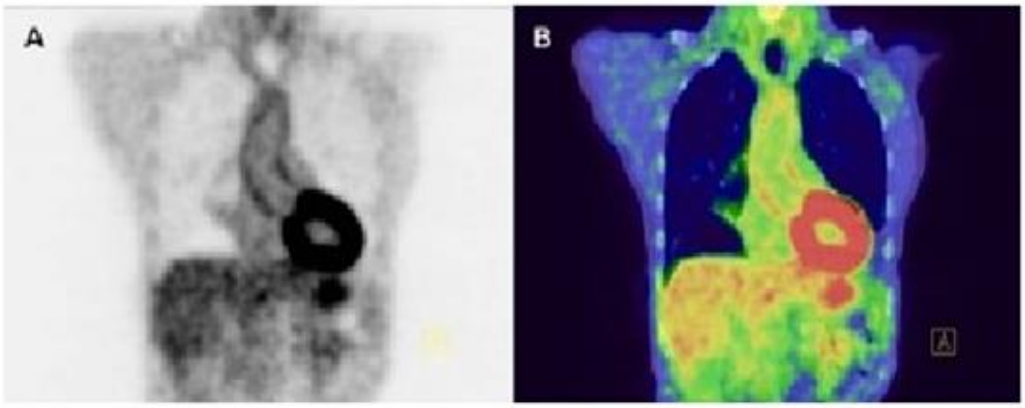
A
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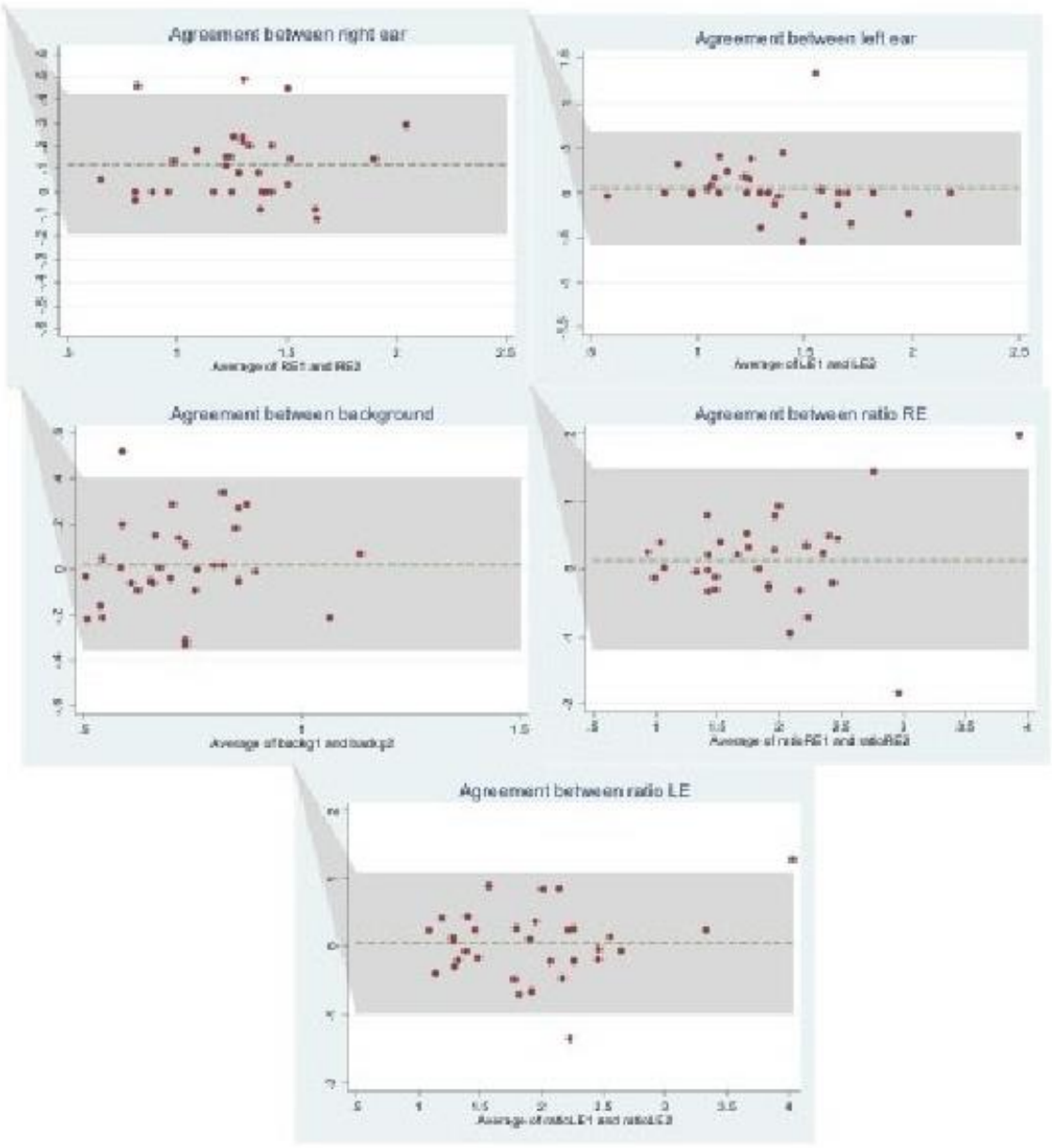
Agreement between right ear
Agreement between left ear
Agreement between background
Agreement between ratio RE
Agreement between ratio LE

Table 1. Clinical manifestations of IMIED. Sensorineural hearing loss (SNHL) is responsive to corticosteroids.

Asymmetric bilateral rapidly progressive SNHL (weeks or months).
Bilateral sudden SNHL (hours to days).
Recurrent sudden SNHL (more than 2 episodes in one year).
Fluctuating SNHL in one ear following inner ear damage in the opposite ear (CMV infection, inner or middle ear surgery, sudden SNHL) (days to years after the event).
Bilateral Meniere´s disease.

Table 2. Systemic autoimmune diseases in secondary IMIED.

Antiphospholipid syndrome	1
Antiphospholipid syndrome + Sjogren syndrome	1
Sjogren syndrome	1
Autoimmune thyroiditis	5
Autoimmune thyroiditis + autoimmune encephalitis	1
Connective disease + celiac disease	1

Table 3. Patients included in the study. *One patient affected by secondary IMIED showed multiple activity. N-number of patients. W-women. M-men.

Primary IMIED	N patients	sex	age	No activity	thyroid	aorta	Waldeyer ring	spine	lung	prostate
	18	10 w 8 m	41.8 15-72	10	2	2	2	2	1	1
Secondary IMIED	N patients	sex	age	No activity	thyroid	aorta	adrenal gland	pituitary gland	uterus	perineum
	10	10 w	47.1 26-58	5	3	2*	1*	1*	1*	1*

group	n	Right ear (RE)	Left ear (LE)	Background (B)	Ratio RE/B	Ratio LE/B
Control	4	1.37 (0.40)	1.377 (0.70)	0.68 (0.17)	1.99 (0.33)	1.95 (0.74)
Primary IMIED	18	1.35 (0.34)	1.32 (0.34)	0.75 (0.19)	1.96 (0.96)	1.91 (0.91)
Secondary IMIED	10	1.30 (0.26)	1.42 (0.19)	0.71 (018)	1.91 (0.52)	2.05 (0.39)

A

group	n	Right ear (RE)	Left ear (LE)	Background (B)	Ratio RE/B	Ratio LE/B
Control	4	1.12 (0.22)	0.92 (0.24)	0.57 (0.16)	2.19 (1.15)	1.72 (0.70)
Primary IMIED	18	1.22 (0.34)	1.34 (0.42)	0.75 (0.17)	1.67 (0.52)	1.84 (0.66)
Secondary IMIED	10	1.23 (0.29)	1.41 (0.33)	0.67 (0.12)	1.89 (0.59)	2.15 (0.59)

B

Table 4. Inner ear measurements performed by each consultant (A and B). Mean and Standard deviation ( ) are shown. n- number of patients.

Table 5. Bland & Altman analysis.

Batplot	Mean difference	Limits of agreement	Averages
Agreement between right ear (RE)	.115937500318978	(-.1873664026340678,.4192414032720238)	0.655 and 2.045
Agreement between left ear (LE)	.0525000012712553	(-.5761488511522573,.681148853694768)	0.580 and 2.180
Agreement between background (B)	.0234374997671694	(-.3528653545342372,.399740354068576l)	0.505 and 1.135
Agreement between ratio RE/B	.1328392176656053	(-1.198995743249829,1.464674178581039)	0.940 and 3.938
Agreement between ratio LE/B	.0538094497751445	(-.9679355200363946,1.075554419586684)	1.093 and 4.031

Table 6. Intraclass Correlation Coefficients (ICCs)

	ICC	(95%	Conf. Interval)
Right ear (RE)	.8278208	.4837779	.9305282
Left ear (LE)	.6443895	.388539	.8085289
Background (B)	.4241236	.0922898	.6707279
Ratio RE/B	.549665	.2582356	.7504987
Ratio LE/B	.7249198	.5076572	.8555285

Less than 0.40—Poor.
Between 0.40 and 0.59—Fair.
Between 0.60 and 0.74—Good.
Between 0.75 and 1.00—Excellent.

Anexo 7

“Immune-mediated inner ear disease: role of new diagnostic tools for its characterization.”

Este es el artículo derivado directamente de lo escrito en este proyecto y sus resultados.

IMMUNE-MEDIATED INNER EAR DISEASE: ROLE OF NEW DIAGNOSTIC TOOLS FOR ITS CHARACTERIZATION

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Running title: Diagnostic tools in Immune-mediated inner ear disease

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ABSTRACT

The main goal of this investigation is to provide a new insight towards possible diagnostic tools such as Magnetic Resonance Imaging (MRI) and PET scan (Positron Emission Tomography) to characterize immune-mediated inner ear disease (IMIED).

A retrospective case review study design analyzing patients with IMIED was performed. 67 patients suspected of having an IMIED (primary or secondary) were studied. Twenty-eight patients referred a sudden hearing loss as form of presentation and 39 a fluctuating hearing loss. Twenty-seven patients underwent an MRI of the temporal bone with previous intratympanic Gadolinium observing endolymphatic hydrops in 13 patients. A PET scan was performed on 30 patients being altered in 17 of them. Initial and treatment for recurrences included mainly corticosteroids: intratympanic, intravenous, oral or the combination of two or three of them.

IMIED lacks a specific serological marker and it may show different clinical presentations, mimicking diverse inner ear disorders. Fluctuating hearing loss has been the most frequent presentation in the present study. IT Gd MRI has reported EH in a group of patients mainly affected by primary IMIED. PET has provided the diagnosis of unknown or underestimated secondary IMIED.

In conclusion, both IT Gd MRI and PET have shown to be diagnostic tools that can facilitate the characterization of this entity.

Key words: intratympanic gadolinium, MRI, PET, immune-mediated inner ear disease, endolymphatic hydrops

No financial disclosures.
The authors report no conflicts of interest.

INTRODUCTION

Immune mediated inner ear disease (IMIED) is a syndrome defined as a sensorineural bilateral hearing loss, usually asymmetric, rapidly progressive along weeks or months responding to corticosteroids or immunosuppressive agents. The hearing loss might appear as unilateral and sudden which would be indistinguishable from a sudden sensorineural hearing loss (SSHL) or fluctuating that when accompanied by vertigo would be very difficult to differentiate from a Meniere's disease. The importance of this type of hearing loss is the fact that it represents one of the few causes of sensorineural hypoacusis that might be reversible with medical treatment. [1-7] IMIED refers to a pathology restricted to the ear (primary IMIED) or to systemic, autoimmune diseases involving the inner ear (secondary IMIED). [8] Primary IMIED is a rare disorder and it represents a challenge for otologists because of the lack of a definitive diagnostic test. [9]

Diagnosis and management are usually dependent on audiometric evaluation and characteristic clinical symptoms. There is no gold standard test for the diagnosis of IMIED, nor is there any test that reliably reflects disease status. The search for a specific diagnostic marker has led the identification of diverse cochlear proteins as immune targets by means of experimental animal models of immune-mediated labyrinthitis. [10, 11]

Imaging cochlear, vestibular, and 8th cranial nerve abnormalities remains a challenge. [1-2] Nevertheless, an example of one outstanding diagnostic tool that might be used for clinical practice and investigation is the Magnetic resonance imaging (MRI) of the inner ear. When enhanced by Gadolinium (Gd), the intention is to reveal the perilymphatic spaces throughout the membranous labyrinth of the scala tympani and scala vestibule and semicircular canals. [2, 3, 9, 12, 13] In-vivo visualization of the enlargement of the endolymphatic space in patients diagnosed with Meniere disease represents a real advance in the diagnosis of this entity and intratympanic Gd MRI could be a useful tool in the study of other inner ear disorders such as IMIED.

On the other hand Positron emission tomography (PET) is an excellent noninvasive diagnostic evaluating tool that operates by using computer reconstruction of cross-sectional images detected by scanner crystals from two photons (gamma rays) released at opposite directions after emission of a positron through decay of radioactive isotopes to create an image. In PET there are various radioisotopes and chemical substrates that might be used such as 18-fluoro-2-deoxyglucose (FDG), which detects glucose metabolism in human tissue. [15-17]

This test might assess disease activity and prognosis in some systemic autoimmune diseases such as systemic lupus erythematosus. For example PET with FDG has demonstrated the possibility to visualize large concentrations of infiltrating granulocytes, tissue macrophages and

activated lymphocytes in lymphoid organs where antigen presentation and lymphocyte activation occur by targeting the increased glucose uptake in these locations. [17]
We hypothesized that FDG can be used in PET to assess different organ activity in patients with IMIED.

The aim of the present study is to assess the role of intratympanic Gd MRI and PET/CT in the characterization of primary and secondary IMIED and the possible inclusion of both tools in the diagnostic algorithm.

PATIENTS AND METHODS

This retrospective clinical study involved 67 patients with suspicion of immune-mediated inner ear disease (IMIED) (47 female and 20 male patients; age range 15-72 years) who visited the Otorhinolaryngology department at "Puerta de Hierro-Majadahonda" University Hospital from January 2014 to December 2016.

This study was approved by the local ethics committee (PI 149-14, Acta 306, 12-01-2015 and PI 15/16, Acta 04.16). Informed consent for the participation in the study was received from all patients.

Primary eligibility inclusion criteria included:

- Patients suspected of having an immune mediated inner ear disease (IMIED) assisted at PHUH from January 2014 to December 2016.
- Subtypes of IMIED:

1. Asymmetric and progressive bilateral hearing loss (weeks to months)
2. Sudden sensorineural hearing loss; more than two episodes within a year (hours to days)
3. Fluctuating unilateral hearing loss secondary to contralateral disease (months to years)
4. Immune-mediated Meniere's Disease (bilateral)

- All of them were responsive to treatment with corticosteroids and/or immunosuppressive agents
- More than 15 years old
- Appropriate mental health in order to understand and assist to consults, follow-up, respond to audiologic testing and approve consents when required (if younger than 18 years old consent is signed by parents or tutors)

Exclusion criteria:

- Patients with any other non-immunemediated hearing loss such as acoustic trauma, ototoxicity, or congenital hearing loss were discarded
- Patients taking medications known to interact with gadolinium contrast agents (chemotherapy and HIV medications) or allergic reactions to gadolinium contrast agents
- Tympanic membrane perforation
- Kidney failure
- Metal foreign bodies and/or pacemakers

Medical history was recorded for all patients. A complete otolaryngologic examination was performed as well as an audiologic evaluation including otomicroscopy and impedance testing. Hearing levels were evaluated with pure-tone audiometry. The pure-tone hearing thresholds (125–8000 Hz) were measured with a manual audiometer (Madsen Orbiter 922, version 2; Madsen Electronics, Taastrup, Denmark) and equipped with TDH-39 supra-aural earphones (Telephonics Co., Farmingdale, NY, USA). Hearing loss has been considered as an average loss of more than 30 dB (500 + 1000 + 2000 + 4000 Hz). The expected conventional frequency pure-tone hearing thresholds of otologically normal subjects are published in ISO 7029 (International Organization for Standardization, 2000).

The Extended High Frequency (EHF) audiometry (9000-20000 Hz) was performed with the same audiometer and Koss HV/1A circumaural earphones. All the audiometric material was calibrated according to the manufacturers' recommendations as well as to ISO 389-112 and IEC 60645-113 standards. The transducers were calibrated according to ISO 389-112 standards.

Every patient received 0.45 -0.9 ml of an intratympanic contrast solution (Gadoteric acid, a gadolinium-based MRI contrast agent. Dotarem® 0.5 mmol/ml injectable solution, Guerbet, Aulnaysous- Bois, France) injected with a concentration of 1/8 (1 ml of gadolinium in 7 ml of normal saline) bilaterally, previous anesthesia of the external ear canal and the tympanic membrane. This method was described previously. [2, 18, 19]
The radiological MRI assessment was performed in the following 24-48 hours with a Philips ACHIEVA 3 T (Best, Netherlands) with an 8 channel SENSE (SENSitivity Encoding) antenna and a 3 D real Inversion recovery (3D-IR) sequence and a 6000 ms repetition time, 107 ms echo time, 1650 ms inversion time, 180◦ inversion angle, number of signal averages (NSA) 1, SENSE factor 1,5 × 1, a visual campus of 160 × 160 × 18 mm, and a voxel size of 0,55 × 0,63 × 1 mm/pixel. The sequence was achieved in an axial plane and it lasted 12.42 minutes.

Two neuroradiologists with 6 and 15 years of experience analyzed the data obtained from each image without knowing the patient's clinical details (blinded). As an anatomic reference to measure the degree of vestibular hydrops the axial plane of the vestibule was chosen, which includes almost all of the lateral semicircular canal. In cochlear hydrops the axial projection centered in a cut plane through the middle plane of the modiolo was used. These anatomic

references helped establish the degrees according to a known scheme. [2, 20, 21] Gadolinium instilled in the middle ear 24 hours before MRI scan allowed a correct imaging contrast and was well tolerated by most of our patients.

According to Barath's criteria, [21] grade I cochlear hydrops was defined as a mild dilation of the non-enhancing cochlear duct, sparing parts of the enhancing perilymph of the scala vestibuli. Grade I vestibular hydrops presented as distention of the endolymph space of the saccule, utricle or both, with the perilymphatic space still visible along the periphery of the bony vestibule. In grade II cochlear hydrops, the scala vestibuli was uniformly obstructed by the maximally distended cochlear duct. In grade II vestibular hydrops, the bony vestibule was entirely encompassed by the dilated endolymphatic spaces.

Presence of vertigo, tinnitus, dizziness and ear pressure were recorded. Systemic diseases such as Wegener, autoimmune thyroiditis, Sjögren disease, inflammatory bowel disease, Cogan's syndrome, Raynaud syndrome, Lupus, Haemochromatosis, antiphospholipid syndrome, Barrett's esophagus and autoimmune encephalitis were accompanying some patients.

PET/CT (with ^{18}F-FDG) was performed to assess systemic involvement as well as inner ear region activity. Interpretation of PET/CT scans was performed independently by two nuclear medicine physicians blinded to clinical history. Before PET scanning, all subjects underwent blood glucose determination; none had hyperglycemia or diabetes.
These images were obtained using a PET/CT system (Biograph 6, Siemens Medical Systems, Knoxville, TN, USA). Six hour fasting before the study was requested to each patient. Acquisition began 60 minutes after the intravenous injection of 370 MBq of 18F-FDG. Imaging protocol included a 1 BED selective image of the base of skull (10 minutes/BED) followed by a standard PET/CT whole body study (4 minutes/BED). Images were reconstructed with a 168x168 matrix using the ordered subset expectation maximum iterative reconstruction algorithm. [15]

Regarding treatment response, it was considered complete when auditory thresholds were classified as normal according to the ISO 7029 (International Organization for Standardization, 2000). Partial response was considered when an improvement in auditory thresholds was demonstrated in a follow-up post-treatment PTA (hearing loss contemplated before as an average loss of more than 30 dB in 500 + 1000 + 2000 + 4000 Hz). No response occurred when there was no improvement at all seen in follow-up PTA.

Statistical Analysis

A descriptive analysis has been performed by means of absolute and relative frequencies for categorical variables and mean (standard deviation), or median (percentiles 25 and 75), minimum and maximum values for numerical variables.

A univariate analysis was made with the Chi-square or Fisher's exact tests for categorical variables and Mann-Whitney test for numerical variables.

All the tests have been performed at a 0.05 level of significance. The statistical software used to perform these analyses has been: Stata v 14.1. (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.)

RESULTS

A total of 67 patients (47 (70.15%) female and 20 (29.75%) male) suspected of having an immune mediated inner ear disease were studied. They were classified by having a primary or a secondary disease. A total of 38 patients presented a primary IMIED and 29 a secondary IMIED. **(Table 1)** Twenty-eight patients referred a sudden sensorineural hearing loss and thirty-nine indicated their hearing loss was fluctuating at the moment of the diagnosis. The subgroups of patients with IMIED were classified as: a. Asymmetric and progressive bilateral hearing loss; b. Sudden sensorineural hearing loss; more than two episodes within a year; c. Fluctuating unilateral hearing loss secondary to contralateral disease; and d. Immune-mediated Meniere's Disease.
Group A includes 14 patients, group B 14 patients, group C accounts for 19 patients and group D includes 20 patients.

All patients underwent bilateral PTA and EHF audiometry. Patients with fluctuating hearing loss including fluctuating unilateral hearing loss secondary to contralateral disease and immune-mediated Meniere's disease presented subjective and clinically assessed recurrent hearing loss. Subjective recurrent hearing loss occurred in a wide range of times varying from 1 to 8 times. On the other hand, recurrent hearing loss that was clinically assessed differed in a smaller grade from 1 to 5 times except for two cases: a male patient with a primary IMIED who presented 9 recurrences and a female patient with Meniere's syndrome with 7 recurrences. Of the 67 patients 39 were classified as having a fluctuating hearing loss of which 80 objective recurrences were recorded. Of the patients that were diagnosed as a sudden sensorineural hearing loss initially, 18 out of 28 presented recurrences classifying them consequently among the fluctuating hearing loss type.

Systemic diseases were described among the patients with a suspected secondary IMIED **(Table 2)**. Other systemic non-autoimmune associations involved Hepatitis C, family members diagnosed of Primary Biliary Cirrosis, and haemochromatosis. One patient presented congenital

cytomegalovirus (CMV) associated with an autoimmune thyroiditis. The patient with autoimmune encephalitis had also vitiligo and autoimmune thyroiditis.

In all the cases studied, the images obtained were valid and of sufficient quality to assess the endolymphatic space. Thirty-eight patients underwent an MRI of the temporal bone with previous intravenous gadolinium (IV Gd) and twenty-seven of them an MRI of the temporal bone with previous intratympanic gadolinium instillation (IT Gd). Of the 38 MRI results with IV Gd 13 of them were altered displaying findings such as anterior inferior cerebellar artery loops, labyrinthitis ossificans, cysts (one arachnoid and one pineal) and small vessel ischemic disease. Regarding IT Gd MRI, endolymphatic hydrops was observed in 13 of 27 patients. **(Table 3)**

A PET scan was performed on 30 patients and was positive in 17 patients (7 with secondary IMIED and 10 with primary IMIED). Minimum FDG uptake was observed in the inner ear of 8 cases. **(Figure 1)** Nevertheless, no significant differences could be established between the normal population and primary or secondary IMIED. Other relevant findings consisted in: six patients with an uptake in the thyroid gland, **(Figure 2)** one patient presented an uptake in the right nasal fossa and nasopharynx, two pulmonary nodules were identified, one in the right mammary gland, two uptakes in the carotid arch, ascending aorta and the supra-aortic trunk, one uptake in the uterus and left ovary, one in the descending aorta, and in one patient uptake was observed in the tonsils and cervical lymph nodes. All of these patients were subsequently studied according to these findings confirming in some cases secondary IMIED.

Immunosuppressive medication or immunomodulatory treatment used involved Methotrexate, Azathioprine, Rituximab, and Adalimumab. Standard pure tone audiometry (PTA) and EHF audiometry was performed before and after immunosuppressive therapy to ascertain positive response to therapy.

Initial treatment applied in our patients included: only intratympanic corticosteroids, intravenous corticosteroids, oral corticosteroids or the combination of two or three of them: 28 (41.79%) of our patients received as an initial treatment only oral corticosteroids, followed by 10 (14.93%) who received a combination of oral and IV corticosteroids and 9 (13.43%) received oral and IT corticosteroids. Nine patients (13.43%) did not receive any initial treatment due to rejection based on possible adverse effects of treatment and "fear" to receive corticosteroid treatment **(Table 4)**. Recurrences were treated with the same possible medications or combinations: 19 (28.36%) of them were treated with oral and IT corticosteroids, and 11 (16.42%) patients only wit IT corticosteroids. In this group 2 patients were treated with oral steroids and Adalimumab and Azathioprine respectively and 2 patients received only immunesuppresive medication. Twenty one (31,34%) patients had no recurrence.

Thirty-two patients had a complete response to initial treatment with full audiological recovery and being symptom free. Nine had a partial response to initial treatment and 8 patients had no response at all.

DISCUSSION

Immune-mediated inner ear disease may present as a localized primary disease when the syndrome refers to a pathology restricted to the ear or it might be found associated with a systemic autoimmune disorder and referred to as secondary accounting for approximately 30% of patients with IMIED. Hughes suggested that hearing loss could begin abruptly, fluctuate over time, and occur associated with vertigo [5, 6]. Primary IMIED is probably an inner ear-specific autoimmune disease involving T-cell targeting of inner ear-specific antigens. On the other hand secondary IMIED may be the consequence, evidenced in the inner ear, of a systemic immune irregularity. Differential diagnoses that must be taken into consideration include cochlear Meniere's and sudden sensorineural hearing loss which are now considered to be associated to autoimmunity. [6, 8, 13, 22-23]

Our patients presented with a sudden SNHL 41.79% (28/67), or a fluctuating SNHL 58.21% (39/67). Eighteen patients (26.8%) presented vestibular symptoms at some point since the onset of symptoms, and only 11 patients (16.4 %) complained of aural fullness. Tinnitus, was a the most frequent complaint as 38 (56.7%) patients claimed it uni o bilaterally. Thirty-two patients had a complete response to initial treatment with full audiological recovery and being symptom free. Nine had a partial response to initial treatment and 8 patients had no response at all. Twenty-five patients had otalgia, usually mild during a couple of hours, after Gd IT application.

The presence of endolymphatic hydrops has been confirmed in a subgroup of patients with IMIED by using MRI with intratympanic gadolinium as a diagnostic tool. This finding corroborates some of the few histopathologic studies performed before in patients with IMIED and raises the idea of the endolymphatic hydrops as an immunopathologic mechanism responsible in patients who have it. [24-26]

The biggest advantage of MRI with IT gadolinium is that the interpretation of the images is simple and requires a quick and short period of learning. It was relatively well tolerated by most patients with very few complications. No deterioration of the hearing function after intratympanic Gd injection has been reported in previous studies of healthy volunteers or patients.

The main inconvenient of this diagnostic tool is the limited availability for intratympanic administration and the extent in time of the sequence which makes it quite sensitive to movement artifacts. [2] Intratympanic administration nevertheless has the advantage of requiring a lower dose of contrast. Normally less than 0.9 ml is needed having an inferior rate of

toxicity. Gadolinium instilled in the middle ear 24 hours before MRI scan gave adequate imaging contrast and was relatively well tolerated by most patients with very few complications. This result is in accordance with several reports as no deterioration of the hearing function of healthy volunteers or patients has been reported after intratympanic Gd injection. [27, 28]

MRI allows a very detailed anatomical approach to the endolymphatic space, almost overlapping direct histologic evaluation. In various histologic and radiologic studies the presence of EH in more inner ear pathology has been demonstrated. The demonstration with MRI of hydrops may be very useful in the diagnosis of inner ear disease that involves vertigo and fluctuating hearing loss. [2, 29]

The difficulty in diagnosing primary IMIED represents a challenge for the otorhinolaryngologist. The use of PET-CT allows us to certify the absence of other affected organs, reinforcing the diagnostic confirmation of a primary IMIED. Secondary IMIED have also been easier to confirm using PET- CT. It may identify any abnormality given by hypo or hypermetabolism of affected ears. Nevertheless, evaluating inner ear metabolic uptake represents a challenge do to the small volume which the inner ear represents. This test could be useful for evaluating autoimmune, inflammatory, or rheumatic disorders. In neurology it has been used for the diagnosis, management, and prognosis of stroke, epilepsy, stroke, Alzheimer's disease, Huntington's disease, Parkinson's diseases, among others. [30, 31]

It has been documented that MRI combined with PET CT may increase the sensitivity of a diagnostic algorithm in autoimmune pathologies.[31] Moreover, PET CT may allow detection of other affected organs in an autoimmune disease and help rule out a primary IMIED and confirm a secondary type. Cochlear or predominantly cochlear hydrops was most often observed in patients with primary disease. EH is observed most frequently in the first place by the saccule, the cochlea, the utricle, and followed by the semicircular canals. [32, 33]

Only 3 patients with secondary IMIED presented endolymphatic hydrops on the MRI. One of them had a congenital CMV infection, the second one an autoimmune thyroiditis and the last one pollinosis (hay fever). In the congenital CMV case it must be noted that it might be a confusing issue due to the fact that it could explain EH by itself. [34]

Although we believe that MRI and PET CT may together allow a more sensitive evaluation of autoimmune pathologies, diagnosis of IMIED is still based on clinical characteristics and response to treatment. No specific immunologic marker for primary IMIED has yet been found although many attempts have been done. [10-11]

EH has been demonstrated in a subgroup of patients with IMIED after using intratympanic gadolinium MR imaging. This suggests the fact that EH may account for an immunopathologic

mechanism responsible for IMIED. Since IMIED is a very rare disorder, the results we provide with our study may help guide future descriptions and support the actual available studies to properly diagnose and treat on time primary and secondary IMIED. MRI and PET-scan are two diagnostic tools that have clearly helped us characterize IMIED.

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TABLE and FIGURE LEGENDS

Table 1: Comparison between primary and secondary IMIED regarding gender, PET results and RM with IT gadolinium results. M-men W-women.

Table 2: Systemic diseases found in patients with IMIED.

Table 3: Comparison between normal, altered or not performed MRIs in patients with previous intravenous gadolinium or intratympanic gadolinium.

Table 4: Treatments administered to patients at the beginning of the first episode of symptoms and during recurrences.

Figure 1: FDG uptake observed in the inner ear in this case, with a standardized uptake value (SUV) of 2.19.

Figure 2: Images showing an FDG uptake in the thyroid gland of a the patient with the inner ear uptake shown in Figure 1.

Table 1

	Gender (M/W)		STEROID RESPONSE				PET			RM Gd IT		
	M	W	No Resp	Partial	Complete	N/A	Normal	Altered	No performed	Normal	Altered	No performed
Primary	18	19	4	10	22	1	7	10	20	8	10	22
Secondary	2	28	4	7	14	5	6	7	17	9	3	18
Total	20	47	8	17	36	6	13	17	37	14	13	40

Table 2

Systemic Diseases	Men	Women
Inflammatory bowel disease		1
Wegener's syndrome		1
Susac's syndrome		1
Autoimmune thyroiditis	1	13
Connective tissue disease		2
Sjogren's syndrome		2
Vitiligo	1	
Raynaud's syndrome		2
Relapsing polychondritis		1
Cogan's syndrome		1
Systemic Lupus Erythematosus		1
Autoimmune encephalitis		1*
Familial Mediterranean fever		1
Pollen Allergy		1

* The patient with autoimmune encephalitis presented vitiligo and autoimmune thyroiditis years later.

Table 3

MRI	IV Gd		IT Gd	
Normal	25	37,31%	14	20,90%
Altered	13	19,40%	13	19,40%
Not performed	29	43,28%	40	59,70%
Total	67	100%	67	100%

Table 4

Initial Treatment	Nº Patients	(%)	Treatment of Recurrences	Nº patients	(%)
ITC	6	8,96%	ITC	11	16,42%
IV CORTICOSTEROIDS	2	2,99%	IV CORTICOSTEROIDS	1	1,49%
ORAL CORTICOSTEROIDS	28	41,79%	ORAL CORTICOSTEROIDS	6	8,96%
ORAL + ITC CORTICOSTEROIDS	9	13,43%	ORAL + ITC CORTICOSTEROIDS	19	28,36%
IV + ORAL CORTICOSTEROIDS	10	14,93%	IV + ORAL CORTICOSTEROIDS	3	4,48%
IV + ORAL CORTICOSTEROIDS + ITC	1	1,49%	IV + ORAL CORTICOSTEROIDS + ITC	1	1,49%
ORAL CORTICOSTEROIDS + ITC + METHOTREXATE	1	1,49%	ORAL CORTICOSTEROID + IMMUNOSUPRESSIVE MEDICATION	2	2,99%
NO INITIAL TREATMENT	9	13,43%	IMMUNOSUPRESSIVE MEDICATION ONLY	2	2,99%